Novel agents in chronic lymphocytic leukemia

Nicole Lamanna[1] and Susan O'Brien[2]

[1]Leukemia Service, Chronic Lymphocytic Leukemia Program, Hematologic Malignancies Section, Herbert Irving Comprehensive Cancer Center, New York–Presbyterian/Columbia University Medical Center, New York, NY; and [2]Chao Family Comprehensive Cancer Center, Sue and Ralph Stern Center for Clinical Trials & Research, Division of Hematology/Oncology, Department of Medicine, University of California, Irvine, Orange, CA

The advent of novel small-molecule inhibitors has transformed the treatment approaches for patients with chronic lymphocytic leukemia (CLL). These therapies are becoming increasingly used in patients with relapsed disease, patients with 17p deletion, and, as of recently, also in the frontline setting for previously untreated patients with CLL. Moreover, many of these are oral therapies that are significantly less myelosuppressive than chemoimmunotherapy. However, these agents have their own set of unique toxicities with which providers must gain familiarity. There is also ongoing development of second-generation agents which have the promise of less toxicity than the US Food and Drug Administration (FDA)–approved compounds. In addition, immunotherapy and the role of the microenvironment are becoming increasingly important and have therapeutic implications in the treatment of patients with CLL. Ultimately, investigators need to evaluate how to position these and other new exciting therapies and decide on the ultimate role for chemoimmunotherapy in modern times.

Learning Objectives

- Review evidence-based treatment approaches for the use of novel B-cell receptor and B-cell lymphoma 2 inhibitors in patients with CLL
- Discuss and describe potential side effects of the emerging therapy options for patients with CLL
- Implement the optimal management for CLL patients with deletion 17p

Introduction/overview

There has been a dramatic change in the treatment of patients with chronic lymphocytic leukemia (CLL) over the past 5 years. The continued understanding of the biology has led to the development of more targeted therapies. Although traditional chemoimmunotherapy programs have been the mainstay of treatment and can achieve complete responses in many previously untreated patients, the enhanced toxicity of these treatments has limited their use to fit younger patients with adequate organ function. The median age of patients with CLL is 72 years, and this has limited the use of more myelosuppressive treatment combinations. In addition, in the relapsed setting, patients may be less likely to respond to chemoimmunotherapy and have increasing infectious complications due to their worsening immune system which limits their therapy.

Our improved appreciation and understanding regarding the heterogeneity of CLL has allowed us to use clinical, biological, and genetic parameters to help risk stratify patients into low-, intermediate-, and high-risk disease. Traditional approaches have focused on targeting the CLL cells as an autonomous malignant population. Our understanding that CLL cell survival is also dependent upon a permissive microenvironment in which there are several influential cellular components such as T cells, macrophages, stromal dendritic cells, and others has further added to the complexity of treatment considerations.[1] In addition, the identification that the B-cell receptor signaling pathway is aberrantly activated has provided several target kinases for which inhibitors have recently been approved by the US Food and Drug Administration (FDA); many others continue to be in development.[2,3] In addition, Bcl-2 has also become a target, given the knowledge that Bcl-2 is an important antiapoptotic protein. These novel agents have shown activity in heavily pretreated patients with CLL as well as in patients with high-risk prognostic features such as 17p deletion. Many of these oral agents also have the added benefit of being generally more tolerable than traditional combination chemoimmunotherapy programs allowing frailer older patients to be treated more easily. This brief overview will discuss these and other potential novel therapies which have reinvigorated the field and will also highlight potential directions for the future (Table 1).

B-cell receptor signaling pathway inhibitors

Bruton tyrosine kinase inhibition

Ibrutinib (PCI-32765). Ibrutinib is the first kinase inhibitor approved for CLL (initially FDA approved in February 2014) and is now approved to treat patients with CLL regardless of their treatment history. Ibrutinib is an orally bioavailable inhibitor that forms a covalent bond with the Bruton tyrosine kinase (BTK) cysteine-481

Conflict-of-interest disclosure: S.O. has received research funding from Pharmacyclics, LLC, an AbbVie Company and has consulted for and received honoraria from Pharmacyclics, LLC, an AbbVie Company and Janssen. N.L. declares no competing financial interests.

Off-label drug use: None disclosed.

Table 1. Novel agents under investigation

Target	Name of agent	Status
Drug class: small-molecule inhibitor		
BTK	Ibrutinib (PCI-32765)	Approved
	Acalabrutinib (ACP-196)	Investigational
	BGB-311	Investigational
	ONO-4059 (GS-4059)	Investigational
PI3K	Idelalisib (GS-1101, CAL-101)	Approved
	Duvelisib (IPI-145)	Investigational
	TGR-1202	Investigational
	Buparlisib (BKM-120)	Investigational
	GS-9820	Investigational
	AMG-319	Investigational
	SAR245408	Investigational
Syk	Fostamatinib (R788, R406)	Investigational
	Entospletinib (GS-9973)	Investigational
Src	Dasatinib	Approved (not in CLL)
Bcl-2	Venetoclax (ABT-199)	Approved
CDK	Alvocidib (flavopiridol)	Investigational
	Dinaciclib	Investigational
	Palbociclib (PD-0332991)	Approved (not in CLL)
Drug class: immunotherapy		
CD20	Rituximab	Approved
	Ofatumumab	Approved
	Obinutuzumab	Approved
CD19	CAR T cells	Investigational
CD19/CD3	Blinatumomab	Approved (not in CLL)
BiTE		
CD37	TRU-016	Investigational
CD37 (ADC)	IMGN529	Investigational
PD-1	Pembrolizumab (MK-3475)	Approved (not in CLL)

BiTE, bispecific T-cell engager.

residue.[4,5] BTK is essential for activation of several pathways contributing to CLL-cell survival, including the AKT, extracellular sign-regulated kinase, and NF-κB pathways. In addition, BTK is essential to chemokine-mediated homing and adhesion of B cells. Preclinical studies have shown that, in primary CLL cells, ibrutinib has proapoptotic, antiproliferative, and stromal inhibitory properties.[4,5] A summary of some of the clinical trial results with ibrutinib is provided in the following paragraphs.

In an early phase 1 trial with ibrutinib, there was no maximum tolerated dose (MTD) reached with mild-moderate toxicity and clinical activity was noted in 56 patients with relapsed, refractory B-cell malignancies.[6] Responses were seen in 60% of the 50 evaluable patients, including complete response (CR) in 16%. Median progression-free survival (PFS) was 13.6 months. This prompted a phase 1b-2 study of ibrutinib in patients with relapsed CLL or small lymphocytic lymphoma (SLL).[7] There were 2 doses used in the 85 patients (51 received 420 mg and 34 received 840 mg daily). The median number of prior therapies was 4; 33% had deletions of 17p and 36% had deletion of 11q. The overall response rate (ORR) was 71% (2 CR and 34 partial responses [PRs]) in the 420-mg cohort and 71% (24 PRs) in the 840-mg cohort. Given the lymphocytosis that occurs concomitantly as the lymph nodes decrease, an additional 15 patients (18%) achieved what is now called PR with persistent lymphocytosis (PRL), meeting all criteria for PR but without a lymphocyte count <50% below baseline. Importantly, the response to ibrutinib did not vary according to traditional high-risk prognostic features. The response rate among patients with deletion 17p was 68%. In addition, durable responses were seen irrespective of dose. The 26-month estimated PFS was 75% and the rate of overall survival (OS) was 83%. Adverse events (AEs) of all grades occurring in at least 25% of patients treated with ibrutinib therapy include diarrhea (49%), upper respiratory tract infection (33%), fatigue (32%), cough (31%), arthralgias (27%), rash (27%), pyrexia (27%), and peripheral edema (27%). Serious grade ≥3 AEs noted in >1% were diarrhea (2%), fatigue (4%), pyrexia (5%), hypertension (5%), sinusitis (5%), and neutropenia (15%).

In the same phase 1b/2 trial, O'Brien et al reported the results of a cohort of previously untreated older patients (>65 years of age) with CLL who received ibrutinib as initial therapy.[8] Twenty-nine patients with CLL and 2 with SLL were enrolled with median age of 71 years (range, 65-84 years) with 23 patients (74%) at least 70 years old. There were 22 responses (71%) seen at a median follow-up of 22 months: 4 patients (13%) had a CR, 1 patient (3%) had a nodular PR, and 17 patients (55%) had a PR.

The phase 3 study comparing ibrutinib to ofatumumab in previously treated patients with CLL (RESONATE-1) published by Byrd and colleagues led to FDA approval of ibrutinib in relapsed disease.[9] Three hundred ninety-one patients were randomized to receive either ibrutinib (420 mg daily) until disease progression or unacceptable toxicity; or ofatumumab for up to 24 weeks at an initial dose of 300 mg at week 1, followed by a dose of 2000 mg weekly for 7 weeks and then every 4 weeks for 16 weeks. Enrollment included 195 patients in the ibrutinib arm and 196 in the ofatumumab arm; the median number of prior regimens was 3 in the ibrutinib arm compared with 2 in the ofatumumab arm. Other baseline characteristics were similar in both arms with ~50% of patients resistant to purine analogs; one-third of patients had either del 17p and 11q. The ORR was 42.6% in the ibrutinib arm vs 4.1% in the ofatumumab arm. At a median follow-up of 9.4 months, ibrutinib significantly improved PFS; the median duration was not reached in the ibrutinib group as compared with a median of 8.1 months in the ofatumumab group. At 12 months, the OS rate was 90% in the ibrutinib arm and 81% in the ofatumumab arm. The efficacy results of this study are not surprising. What is important to note is that the presence of a control arm allowed further delineation of uncommon ibrutinib-related side effects such as atrial fibrillation. AEs were similar between the 2 arms except those grade 3 or higher that occurred more frequently in the ibrutinib arm included (diarrhea 4% vs 2%) and atrial fibrillation/cardiac disorders (7% vs 3%). In addition, bleeding events of any grade (petechiae, ecchymoses) were more common in the ibrutinib arm (44% vs 12%) with major hemorrhage defined as resulting in transfusion or hospitalization similar between the 2 arms (1% vs 2%).

The approval of ibrutinib in previously untreated patients with CLL is based on data from the randomized, multicenter, open-label phase 3 RESONATE-2 trial, which evaluated the use of ibrutinib vs chlorambucil in 269 treatment-naive patients with CLL/SLL aged 65 years or older.[10] Patients were randomly assigned to receive

either ibrutinib (420 mg once daily) until disease progression or unacceptable toxicity or up to 12 cycles of chlorambucil (given at a dose of 0.5 mg per kilogram of body weight on days 1 and 15 of each 28-day cycle, which was increased to a maximum of 0.8 mg per kilogram, if tolerable). The ORR was higher with ibrutinib than with chlorambucil (86% vs 35%). Ibrutinib resulted in significantly longer PFS than did chlorambucil (median, not reached vs 18.9 months), with a risk of progression or death that was 84% lower with ibrutinib than that with chlorambucil. Ibrutinib significantly prolonged OS with the estimated survival rate at 24 months of 98% with ibrutinib vs 85% with chlorambucil. Although the randomized trial was designed for an older population of patients, and used what would arguably be a less attractive control arm for younger fit patients, the FDA frontline approval is not age-restricted. Two Intergroup trials compared fludarabine, cyclophosphamide, and rituximab or bendamustine and rituximab to ibrutinib-based therapy. These trials are fully accrued but no data are yet available.

The addition of other agents to ibrutinib may abrogate the lymphocytosis seen with ibrutinib alone and further increase the ORR. A phase 2 study of ibrutinib in combination with rituximab in high-risk patients with CLL was reported by Burger and colleagues.[11] High risk in this study was defined as patients with the deletion 17p, TP53 mutation, deletion 11q, or a short PFS (<36 months) after previous first-line chemoimmunotherapy. A total of 40 patients who had received a median of 2 prior therapies (range, 1-4) were treated. Patients received ibrutinib 420 mg once daily plus weekly rituximab (375 mg/m^2) for weeks 1 to 4, then monthly until cycle 6. Ibrutinib was continued until disease progression or unacceptable toxicity. The combination produced an ORR of 95% with a CR rate of 10%. At a median follow-up of 18 months, 31 patients (78%) remained on ibrutinib with a PFS of 78% and an OS rate of 84%. In the 20 patients with either TP53 or del17p, the combination resulted in a 90% ORR. Although it was clear that adding rituximab to ibrutinib resulted in markedly faster responses, whether more deeper or durable remissions occur is unclear. An ongoing randomized trial of ibrutinib ± rituximab may provide an answer.

In an effort to look at the combination of ibrutinib with chemoimmunotherapy, Brown et al reported on the combination of ibrutinib with bendamustine and rituximab (BR) in relapsed patients with CLL.[12] The median number of prior therapies was 2 (range, 1-3); 43% and 23% of patients had del 17p and 11q, respectively. Patients received up to 6 cycles of BR with a continuous ibrutinib dose of 420 mg per day. Bendamustine was administered at 70 mg/m^2 on days 1 and 2 combined with rituximab 375 mg/m^2 on day 1 for cycle 1 and 500 mg/m^2 on day 1 for subsequent cycles. Ibrutinib dosing continued until disease progression or other reason for discontinuation. The ORR in 30 patients was 93% which included 5 CRs and 3 nodal PRs. The median PFS was not yet reached and the estimated PFS at 12 months was 90%.

In order to evaluate whether this combination was better than BR alone, a phase 3 study, known as the Helios trial, randomized relapsed patients with CLL to BR with or without the addition of ibrutinib.[13] This large trial randomized 289 patients to each arm; the median number of prior therapies was 2. Estimated PFS at 18 months was significantly longer with ibrutinib plus BR vs placebo plus BR (79% vs 24%) and results were consistent across high-risk subgroups. The median OS was not reached. Ninety patients (31%) in the placebo plus BR arm with subsequent progression crossed over to receive ibrutinib. The incidence of most AEs was similar between arms with a slight increase in rates of grade 3/4 atrial fibrillation (2.8% vs 0.7%) and major hemorrhage rates (2.1% vs 1.7%) in the ibrutinib plus BR arm. It is clear that the addition of ibrutinib enhances the PFS produced by BR compared with that seen with BR alone. What is less obvious is whether the PFS would have been much different from ibrutinib monotherapy (given that the estimated PFS at 30 months was 69% in the updated phase 2 study).[14]

Other BTK inhibitors. Some of the side effects of ibrutinib that can necessitate dose reductions or cessation of therapy include arthralgias, fatigue, ecchymosis/bleeding, and atrial fibrillation. There are several second-generation small-molecule inhibitors of BTK which have shown excellent clinical activity and the promise of an improved toxicity profile (by being more BTK selective). The ones furthest along in clinical development include acalabrutinib (ACP-196), BGB-311, and ONO-4059.

In a phase 1-2 study, acalabrutinib was studied in 61 patients with relapsed CLL. Patients were treated at a dose of 100 to 400 mg daily.[15] In the expansion (phase 2) cohort, patients were treated at 100 mg twice daily. The median number of previous therapies for CLL was 3; 31% had 17p deletion. No dose-limiting effects occurred during the dose-escalation portion. At a median follow-up of 14.3 months, the ORR was 95%, including 85% with a PR and 10% with a PRL. All patients with 17p deletion responded. The most common AEs were headache, diarrhea, and increased weight. No atrial fibrillation or severe bleeding was noted.

Tam et al recently presented the results of a phase 1 study of BGB-3111 in 39 patients with relapsed refractory B-cell malignancies (14 of these patients had CLL).[16] Patients were enrolled in 1 of 5 dose cohorts (40, 80, 169, 320 mg daily; 160 mg twice daily). No dose-limiting toxicities were encountered and the MTD was not reached. The recommended phase 2 dose was 320 mg daily. The ORR was 93% (13 of 14) in the CLL cohort; all PRs. There were no drug-related serious adverse events (SAEs) reported at this early presentation.

A phase 1 study of ONO-4059 was reported in 25 relapsed patients with CLL, doses ranged from 20 to 600 mg daily for up to 2 years and upon completion of the first 6 months of treatment, intrapatient dose escalation was permitted.[17] Patients received a median of 4 prior therapies (range, 2-8); 8 of 22 (36%) had deletion 17p and 6 of 22 (27%) deletion 11q. The ORR was 90% in 21 of 25 evaluable patients with 14 PRs and 5 PRL. The median duration of treatment was 270 days (range, 1-540 days) with 22 of the 25 patients remaining on treatment. There was no evidence of a dose-response relationship and no dose-limiting toxicities thus far. ONO-4059 was acquired by Gilead and is now called GS-4059; it is in a phase 1 trial in combination with entospletinib, a SYK inhibitor, in patients with B-cell hematologic malignancies.

Additional studies with these BTK inhibitors are ongoing. Whether these agents provide greater efficacy or less side effects than ibrutinib remains to be seen.

Phosphatidylinositol 3-kinase inhibition

Idelalisib (GS-1101; formerly CAL101). Idelalisib is the second B-cell receptor inhibitor FDA approved (in combination with rituximab in July 2014) in patients with previously treated CLL. It is a potent, oral, selective inhibitor of the phosphatidylinositol 3-kinase (PI3K) δ isoform (PI3Kδ). The δ isoform is highly expressed in

lymphoid cells and believed to be one of the critical isoforms involved in the malignant phenotype in CLL. It is needed to activate the serine-threonine kinases AKT and mammalian target of rapamycin and exerts pleiotropic effects on cell metabolism, migration, proliferation, survival, and differentiation as well as possibly exerting a role in other surface receptors that impact CLL pathophysiology (such as CXCR4, CD40, and CD49d).[18-23]

In a phase 1 study exploring single-agent idelalisib at doses ranging from 50 to 350 mg (daily or twice-daily administration) in 54 patients with relapsed CLL, there were no dose-limiting toxicities.[24] Patients were heavily pretreated with a median of 5 prior therapies (range, 2-14), and had other high-risk features including bulky lymphadenopathy (80%), refractory disease (70%), unmutated IGVH (91%), del 17− and/or TP53 mutation (24%), and deletion 11q (28%). The ORR was 72%, with 39% (39 of 54) achieving a PR and 33% (18 of 54) a PR with lymphocytosis. The median duration of response was 16.2 months and the median PFS for all patients was 15.8 months; the median OS was not reached, with 75% of patients surviving at 36 months. The median PFS for patients (n = 28) treated at ≥150 mg twice daily (the recommended dose) was 32 months compared with 7 months for those (n = 26) treated at lower doses. The most common AEs with idelalisib of any grade seen in at least 20% of patients included fatigue (31%), diarrhea (30%), pyrexia (28%), transaminitis (28%), rash (22%), upper respiratory infections (22%), and pneumonia (22%) with the most common grade ≥3 toxicities being fatigue (2%), diarrhea (6%), pyrexia (4%), transaminitis (2%), and pneumonia (20%).

To evaluate idelalisib as initial therapy, 64 treatment-naive older patients with CLL (median age, 71 years) were treated with rituximab 375 mg/m^2 weekly for 8 weeks and idelalisib 150 mg twice daily for 48 weeks.[25] Those completing 48 weeks without progression could continue to receive idelalisib on an extension study. ORR was 97% with 19% CRs and PFS was 83% at 26 months. Despite these excellent responses, the most frequent (>30%) AEs were diarrhea/colitis (64%, with 42% grade ≥3), rash (58%), pyrexia (42%), nausea (38%), chills (36%), cough (33%), fatigue (31%), and transaminitis (67%; 23% grade ≥3). The incidences of diarrhea/colitis were higher than observed with single-agent idelalisib that was reported in relapsed refractory CLL patients.

In another phase 1 study, idelalisib was given at 150 mg orally twice daily in combination with rituximab (375 mg/m^2 every week for 8 weeks), bendamustine (70 or 90 mg/m^2 daily for 2 days, every 4 weeks for 6 cycles), or BR (every 4 weeks for 6 cycles) in patients with relapsed refractory CLL.[26] Patients still on treatment after 48 weeks were eligible to continue idelalisib on an extension study. Fifty-two patients were enrolled and disease characteristics included bulky lymphadenopathy (62%), refractory disease (50%), and median prior therapies received 3 (range, 1-14) with 96% having had prior rituximab and 44% having had prior bendamustine. The ORR was 81% with 1 CR. The median time to response was 1.9 months and the 2-year PFS and OS were 62% and 85%, respectively. The median treatment duration was 18 months with 60% of patients enrolled into the extension study. Side effects were similar to those previously reported with idelalisib

The phase 3 study of idelalisib plus rituximab vs placebo plus rituximab in relapsed patients with CLL led to the FDA approval of the combination.[27] Patients were unable to undergo chemotherapy either due to decreased renal function, prior therapy-induced myelosuppression, or major coexisting illnesses or reduced performance status. The study was stopped early due to favorable results seen in the rituximab plus idelalisib arm. All 220 patients were randomized to receive either rituximab (375 mg/m^2 initially followed by 500 mg/m^2 every 2 weeks × 4 doses, then every 4 weeks × 3 doses, for a total of 8 infusions) plus idelalisib (150 mg twice daily) or rituximab (at the same schedule) plus placebo twice daily. Seventy-eight percent of patients were 65 years of age or older (median age in both arms was 71 years) with a median of 3 prior regimens, 40% had moderate renal dysfunction (creatinine clearance <60 mL per minute), 35% had poor bone marrow function (≥grade 3 anemia, thrombocytopenia, or neutropenia), 85% had a Cumulative Illness Rating Scale (CIRS) score of >6 (median was 8 in each arm), >80% had unmutated IGHV, and >40% had 17p deletion or TP53 mutations. At the time of the analysis, the median time that patients received the study drug was short at 3.8 months (0.3-16+ months) and 2.9 months (0.1-14.6 months) in the placebo arm. At the time of study termination, 81% of patients in the idelalisib arm were still receiving the study drug compared with only 52% in the placebo group. The most common reason for discontinuation of the study treatment was disease progression (12 patients in the idelalisib arm vs 53 patients in the placebo arm). The median duration of PFS was not reached in the idelalisib arm vs 5.5 months in the placebo arm. Responses were seen among all patients in the idelalisib plus rituximab arm regardless of unfavorable characteristics such as 17p deletion, TP53 mutations, or IGHV mutational status. The ORR was evaluated for 176 patients (88 patients in each arm) at the time of the analysis and was 81% in the idelalisib plus rituximab vs 13% in the placebo plus rituximab arm. All responses were PRs. The OS in the idelalisib plus rituximab group was 92% vs 80% in the placebo plus rituximab group at 12 months (P = .02). The median duration of OS in the 2 groups has not yet been reached. There was no significant difference in the rate of AEs with the addition of idelalisib to rituximab as compared with placebo and rituximab except for the incidence of transaminitis. Grade 3 or higher transaminase elevation were noted in 6 patients (5%) in the idelalisib plus rituximab cohort but this did not lead to study discontinuation. Interestingly, the infusion reactions seen with rituximab seemed to be less common in patients receiving idelalisib than in patients receiving placebo. This study highlights that rituximab given as a single agent (which is often done in older, frailer patients with CLL in the United States) yields low response rates and there are now many other therapies available for this population.

Most recently, Zelenetz et al presented the results of a phase 3 randomized study of idelalisib plus BR vs placebo plus BR in relapsed patients with CLL.[28] Two hundred seven patients were randomized to the idelalisib plus BR arm and 209 patients to the placebo plus BR arm: age (58%/42% [<65 years/≥65 years]); Rai stage III/IV (46%); median time since completion of last prior therapy (16 months); patients with high-risk features (del(17p)/p53mut [32.9%], unmutated IGHV [83.2%], refractory [29.8%]); median number of prior therapies (2 [range, 1-13]); and median follow-up (12 months). Median number of cycles of BR completed in the 2 arms was equal (6). Median PFS of idelalisib plus BR vs placebo plus BR (23 vs 11 months). Median OS was not reached for either arm. Transaminase abnormalities were observed more frequently in the idelalisib plus BR vs BR plus placebo arm (grade ≥3: alanine transaminase, 21.3%/2.9%; aspartate transaminase, 15.5%/3.3%). Similar to the results noted in the Helios study, it is unclear whether the combination of idelalisib plus BR is ultimately an

improvement in CLL therapy over results seen with idelalisib and rituximab.

Most recently, Gilead Sciences has stopped 6 clinical trials with idelalisib in combination with other agents in the previously untreated setting due to a higher rate of SAEs noted, namely infectious complications with increased deaths seen in the arms with idelalisib. At this point in time, it appears that idelalisib will not be further developed as part of initial therapy in the treatment of CLL.

Other PI3K inhibitors. The common side effects of idelalisib that can be dose-limiting include rash, diarrhea, colitis, increased transaminase levels, and, rarely, pneumonitis. There are several other PI3K molecules in development. IPI-145 (duvelisib) is an oral, potent PI3Kδ, γ inhibitor. Flinn et al reported the results of a phase 1 study of IPI-145 in hematologic malignancies which included 44 relapsed/refractory CLL patients.[29] The median age was 67 years (range, 51-82 years), with 33 (75%) having had ≥3 prior therapies. Thirty-two patients (44%) had TP53 mutation and/or 17p deletion. Twenty-three patients received ≤25 mg twice daily (median number of cycles, 5.6 [range, 1-21]) and 21 patients received 75 mg twice daily (median number of cycles, 3.6 [range, 1-6]). Clinical activity was observed with ORR frequency of 52% with 1 CR, 15 PRs. Notably, PR with lymphocytosis was not included as a response in this analysis. The most common grade 3 AEs were neutropenia (20%), anemia (9%), febrile neutropenia (7%), pneumonitis (7%), and transaminase elevation (5%). The most frequent AEs were respiratory and/or infectious events which occurred in 11 patients (25%).

TGR-1202 is another next-generation PI3Kδ inhibitor that has demonstrated activity in patients with advanced hematologic malignancies. Updated safety and efficacy results were presented at the 2015 American Society of Hematology (ASH) annual meeting from a phase 1 trial of TGR-1202 in patients with relapsed CLL and lymphoma.[30] Seventy-five patients with various histologies were evaluable with a median age of 65 years (range, 22-85 years); they were 67% male, with Eastern Cooperative Oncology Group (ECOG) 0/1/2 scores of 26/47/2, with median prior regimens of 3 (range, 1-14), and 49% were refractory to prior therapy. No grade ≥3 AEs were observed in ≥10% of patient. AEs (all grades, all causality) in >20% of patients were limited to nausea (44% [grade 3/4, 0%]), diarrhea (36% [grade 3/4, 1%]), and fatigue (31% [grade 3/4, 3%]). Although the long-term follow-up is shorter than that of other PI3K inhibitors, the incidence of hepatotoxicity and colitis appears to be much less than that reported with other agents in this class. Of 16 evaluable patients with CLL, 15 (94%) achieved a nodal PR (median nodal decrease of 76%), of whom 10 (63%) achieved a PR. Of the 24 patients starting TGR-1202 at 800 mg or 1200 mg, 19 (79%) remained on therapy, with 9 of 18 (50%) evaluable patients (6 too early to evaluate) achieving an objective response to date (range on study, 3-49+ weeks).

SYK inhibition

Syk (spleen tyrosine kinase) is another protein tyrosine kinase that, when activated, phosphorylates several intermediates that then affect downstream signaling pathways responsible for cell survival and proliferation. Previous in vitro studies as well as an earlier clinical trial reported with the first-in-human Syk inhibitor R406 (fostamatinib or R788) revealed that disrupting this signaling led to clinical activity.[31,32] Friedberg et al reported on a phase 1/2 study in patients with relapsed B-cell malignancies that included 11 CLL patients who had the highest response rate (55%).[33] R406, however, had limited specificity toward Syk and also displayed activity against other kinases.[34]

Entospletinib (GS-9973) is an orally bioavailable selective inhibitor of Syk. Sharman and colleagues described the results of a phase 2 trial of GS-9973 in patients with previously treated CLL or lymphoma.[35] All patients were treated with GS-9973 (800 mg twice daily). Patients with CLL/SLL received a median of 2 prior regimens. Among patients with CLL who received at least 8 weeks of GS-9973 monotherapy, 97% (n = 28/29) experienced a reduction in lymph node size. Twenty (69%) of the 29 patients included in the efficacy analysis achieved >50% tumor shrinkage, including 4 of 7 patients with a chromosome 17p deletion and/or a mutation in the TP53 gene. Overall, GS-9973 was well tolerated. Grade 3 or higher fatigue was reported in 5 patients (6%), and reversible grade 3 or higher transaminase elevations were reported in 9 patients (12%). Eleven patients (14%) discontinued treatment because of AEs.

A recent phase 2 study was the first to evaluate a combination of B-cell receptor inhibitors and evaluated the combination of idelalisib and entospletinib. There was an increased incidence of pneumonitis (compared with that seen with idelalisib alone) with 2 fatalities[36] resulting in termination of the study. Careful evaluation of trial design is needed when combining novel agents.

Bcl-2 inhibition

The Bcl-2 family of regulatory proteins (Bcl-2, Bcl-xL, and Mcl-1) regulate apoptosis by either inducing (proapoptotic) it or inhibiting it (antiapoptotic).[37] Overexpression of antiapoptotic genes and underexpression of proapoptotic genes can result in the lack of cell death that is often characteristic of various cancers. Bcl-2 is an important antiapoptotic protein and damage to the Bcl-2 gene has been identified as a cause of a number of cancers as well as a cause of resistance to cancer treatments.[38-40] A pan-Bcl-2 family inhibitor (BH3 mimetic) has been tested in clinical trials. Navitoclax, an inhibitor of Bcl-2, Bcl-w, and Bcl-xL, was noted to have clinical efficacy; however, its use was limited due to the concomitant on-target thrombocytopenia caused by Bcl-xL inhibition.[41]

Reengineering of navitoclax to create a highly potent, orally bioavailable, and Bcl-2–selective inhibitor, venetoclax (ABT-199), with decreased affinity for Bcl-xL, has resulted in less thrombocytopenia. Initially, ABT-199 showed encouraging clinical activity but an increased risk of tumor lysis syndrome was noted requiring dose modifications, careful monitoring, and slower dose escalation. Seymour and colleagues reported results from a phase 1, open-label, dose-escalation study in 67 patients with CLL/SLL.[42] The initial dosing schema started with a 50-mg dose of ABT-199 during week 1, followed by a 2-step dose escalation. During the second dose escalation from 150 mg to 1200 mg, there was 1 death attributed to tumor lysis syndrome. The study was temporarily suspended and a more conservative 3-step dose escalation (starting with a 20-mg test dose on day 1 with escalation only allowed in absence of biochemical tumor lysis) was performed along with enhanced prophylactic measures. In the 67 patients, the median number of prior therapies was 4 (range, 1-11). Eighty-eight percent of patients (50 of 57) had at least a 50% reduction in lymphadenopathy; the median time to 50% reduction was 6 weeks (the time of the first computed tomography scan stipulated per protocol). Eighty-nine percent of patients (33 of 37) had at least a 50% reduction in bone marrow infiltrate at the first bone marrow biopsy at

week 24. The median time to a 50% reduction in the peripheral blood lymphocyte count (for those with a lymphocyte count >5 at baseline) was rapid at 15 days. The ORR among all evaluable patients was 84%, including 23% CRs. The ORR among patients with del17p was 82% and among those with fludarabine-refractory disease was 89%. No significant episodes of tumor lysis were noted after the dose-escalation modification.

Ma et al presented the results of a phase 1b study of venetoclax in combination with rituximab in relapsed, refractory CLL patients.[43] Forty-nine patients (median age, 68 years; median prior regimens, 2; 20% with del17p; 70% with unmutated IgHV) underwent dose escalation as noted in the previous paragraph. ORR was 86% with 47% achieving a CR/CR with incomplete bone marrow recovery, 2% nodular PR, 39% PR, 8% had stable disease (SD), and 4% had progressive disease (PD). Importantly, minimal residual disease (MRD) negativity in the bone marrow was observed in 55% and 11 patients were able to stop venetoclax after achieving CR/CRi. Nine patients who were MRD^- have not progressed off therapy. The 2 patients who were MRD^+ had asymptomatic progression and restarted therapy with venetoclax. This study highlights an important difference with this agent compared with BTK or PI3K inhibitors which is that there is a higher frequency of CR and a significant proportion of patients can achieve MRD negativity. This will be important in clinical trial development as some combination strategies will evaluate whether MRD negativity can be used as a parameter for drug discontinuation with these novel therapies.

Recently, the combination of venetoclax and obinutuzumab demonstrated safety and activity.[44,45] In addition, Jones et al reported on the use of venetoclax in patients who were intolerant or resistant to a BTK or PI3K inhibitor.[46] Twenty-eight patients were enrolled in this study: 22 entered into arm A after a median duration on ibrutinib of 15.5 months (range, 1-56 months); 6 entered into arm B after a median duration on idelalisib of 9.7 months (range, 1-34 months). At this early report, the median time on venetoclax was 2.4 months (range, 0.1- 7 months) in arm A and 1.7 months (range, 1.2-4.5 months) in arm B. Fifteen patients in arm A and 3 in arm B underwent a week 8 response assessment. In arm A, 8 of 15 (53%) achieved a PR, 6 of 15 (40%) had SD, and 1 of 15 was inevaluable. In arm B, 2 of 4 achieved a PR, 1 of 4 had SD, and 1 of 4 had PD prior to first assessment. Patients with SD had evidence of ongoing disease reduction, measured by decreasing circulating lymphocytes and lymph nodes. No new safety signals for venetoclax were observed in either treatment arm. Although the study is quite early, it will be important to evaluate whether venetoclax can salvage patients who fail therapy with B-cell receptor inhibitors.

In April 2016, venetoclax was approved for relapsed patients with CLL and a 17p deletion who had at least 1 prior therapy based on the data of an open-label, multicenter clinical trial of 106 previously treated patients with 17p deletion.[47] In the study, patients received venetoclax via a weekly ramp-up schedule starting at 20 mg and ramping to 50 mg, 100 mg, 200 mg, and finally 400 mg once daily. Patients continued to receive 400 mg of venetoclax once daily until disease progression or unacceptable toxicity. The median time on treatment at the time of evaluation was 12.1 months (range, 0-21.5 months). The primary efficacy end point, ORR, was 80%. Median duration of response had not been reached with ~12 months of median follow-up (range, 2.9-19.0+ months).

Monoclonal antibodies

Rituximab was the first anti-CD20 monoclonal antibody (mAb) approved for the treatment of hematologic malignancies in 1997. Since then, several other anti-CD20 mAbs have been evaluated in CLL. A phase 3 study evaluated obinutuzumab (a glycoengineered type II antibody) with chlorambucil vs rituximab with chlorambucil or chlorambucil alone in previously untreated patients with CLL and comorbidities.[48] Results demonstrated a superior ORR and PFS with obinutuzumab plus chlorambucil (77% and 26.7 months) compared with rituximab plus chlorambucil (66% and 15.2 months) or chlorambucil alone (31% and 10.7 months). This led to the approval of obinutuzumab plus chlorambucil as frontline therapy in CLL. Similarly, the COMPLEMENT study evaluated ofatumumab (fully human mAb) and chlorambucil vs chlorambucil alone.[49] Given the favorable results of this combination vs chlorambucil monotherapy, ofatumumab plus chlorambucil was also approved for this patient population.

Other novel therapies for CLL

CLL cells have been able to evade the immune system of their host through a variety of mechanisms. Over the past several years, investigators have been able to design a chimeric antigen receptor (CAR) that redirects T cells to tumor-associated antigens, in most cases CD19, expressed on the surface of CLL cells. The CAR T cells then target the CD19 cell surface antigens on CLL cells causing lysis of these cells.[50-52] There have been several reports of this modality inducing remissions in patients with CLL, lymphoma, and acute lymphoblastic leukemia. Limitations have included a potential life-threatening complication via a cytokine-mediated syndrome which can cause fever, hypotension, renal failure, and capillary leak syndrome. Neurologic side effects are also seen. B-cell aplasia and hypogammaglobulinemia are other potential complications. Given the significant responses seen with this approach, ongoing investigations are evaluating ways to maximize the antitumor efficacy of CAR T-cell therapy while evaluating mechanisms to reduce the associated toxicities.

By the same token, novel immunotherapy which blocks the immune checkpoint PD-1 receptor in order to activate cytotoxic T cells has demonstrated remarkable clinical results in solid tumors. Both PDL1 and PD-1 are known to be highly expressed on CLL leukemic cells, CLL T cells, and in the CLL microenvironment. Early data were recently presented from a trial evaluating a PD-1 inhibitor, pembrolizumab (MK-3475), in relapsed patients with CLL including those with Richter transformation (RT).[53] In this study, pembrolizumab was given as 200 mg IV day 1 of each cycle every 3 weeks until progression, excessive toxicity, or completion of 2 years of therapy. Twenty patients were included with a median age of 71 years (58-81 years); median number of prior therapies was 3 (1-6). All patients had received chemoimmunotherapy (fludarabine, cyclophosphamide, rituximab/ pentostatin, cyclophosphamide, rituximab); 4 of 5 RT patients had received anthracycline-containing chemotherapy; 5 of 8 patients had failed prior ibrutinib therapy; 8 patients had 17p−/TP53 mutation. The median number of cycles administered was 4 (3-7). Most patients tolerated pembrolizumab well. Impressively, 4 of 5 patients with RT responded to therapy: 1 patient had a CR after 2 cycles and remains in remission; 1 patient had almost complete positron emission tomography response after 2 cycles and was classified as PR as bone marrow had not been reevaluated yet; 2 patients had responses with nodal and skin lymphoma improvements

Table 2. How I treat

	Treatment
Patients with 17p deletion	These patients (whether de novo or relapsed) should be offered a clinical trial or receive ibrutinib as initial therapy. The PFS for ibrutinib used in patients with relapsed 17p deletion was 28-32 mo, significantly better than any prior therapy (FCR, alemtuzumab alone, or with steroids) used as frontline treatment of such patients. In the relapsed setting, both venetoclax and idelalisib with rituximab are available. There is no role for chemotherapy in the treatment of patients with CLL and 17p deletion.
Patients with previously untreated disease	These patients have many options including chemoimmunotherapy (FCR, BR, and chlorambucil plus obinutuzumab or ofatumumab) as well as ibrutinib. Three recent publications have suggested that FCR resulted in long-term PFS with a plateau on the PFS curve for patients with mutated IGVH, and particularly in those with mutated IGVH and trisomy 12. Thus, in fit patients with good prognostic features, a discussion of the pros and cons of chemoimmunotherapy vs ibrutinib is important. In addition to discussion of short-/long-term efficacy as well as toxicity, the difference in time on therapy is another important component to the discussion.
Previously treated patients	These patients have several options. One should consider their prior therapy, cytogenetics, comorbidities, as well as the side effects of the additional therapies being considered. FISH should always be obtained prior to initiating a new therapy. If previously treated with chemoimmunotherapy, then a small-molecule inhibitor is recommended. Choices include: ibrutinib, idelalisib and rituximab, and venetoclax for those with a 17p deletion. If patients received ibrutinib as frontline therapy (a rare group currently but expected to become more common), then considerations may be dependent on their age/comorbidities and FISH results and could potentially include chemoimmunotherapy, idelalisib + rituximab, and venetoclax.
All patients with CLL	Clinical trials for all patients with CLL should always be considered.

FCR, fludarabine, cyclophosphamide, rituximab; FISH, fluorescence in situ hybridization.

before they showed potential evidence of PDs. The remaining patients had SD and continued on therapy at the last follow-up.

There is continued development of mAbs in addition to the development of antibody drug conjugates (ADCs) which combine a mAb with specificity for a tumor-specific antigen with no, or limited, expression in normal tissues, with a highly potent cytotoxic chemical.[54] Bispecifics comprise a diverse group of mAb-based therapeutics that can have multiple, functionally different, binding domains within the same construct that allow for interaction with 2 target antigens. BiTE antibodies comprise fusion proteins consisting of 2 single-chain variable fragments of different antibodies arranged in tandem on a polypeptide chain. Bispecific antibodies and antibody fragments in various formats have been explored as a means to recruit cytolytic T cells to kill tumor cells. Encouraging clinical data has been reported with molecules such as the anti-CD19/CD3 BiTE blinatumomab.[55,56] There are several others currently in development for B-cell malignancies as well.

Future directions/Conclusion

It is truly an exciting time for patients with CLL and investigators who treat patients with CLL. One new CD20 antibody and 3 oral therapies have been approved in a 2- to 3-year span and there are many others in clinical development. With all of these therapies there is still much work to be done. How to properly use many of these new therapies in combination with other agents (whether other novel agents or more traditional cytotoxics), how to sequence these agents, and whether we can have "drug-free" periods are all areas of active investigation (please see Table 2 for considerations of "How I Treat"). Given some of the specialized toxicities associated with these novel therapies, there is still not a "one size fits all" for patients. In addition, recognition of the pharmacoeconomic implications of lifelong therapy with these oral therapies is important and puts more emphasis on designing combinations that can achieve deeper remissions and allow the possibility of drug discontinuation. Clinical trials will focus on combinations that may be able to exploit drug discontinuation if deep remissions are achieved. In addition, the role of immune checkpoint inhibition in CLL must be investigated, although its utility may be limited in patients who are immunodeficient at baseline. Paramount to our desire to develop new agents and achieve greater clinical efficacy, we must be mindful of the potential short- and long-term toxicities as we develop new combination therapies that incorporate novel compounds.

Correspondence

Nicole Lamanna, Herbert Irving Comprehensive Cancer Center, New York–Presbyterian/Columbia University Medical Center, New York, NY 10032; e-mail: nl2129@mail.cumc.columbia.edu; and Susan O'Brien, Division of Hematology/Oncology, Department of Medicine, University of California, Irvine, Orange, CA 92868; e-mail: obrien@uci.edu.

References

1. Burger JA, Ghia P, Rosenwald A, Caligaris-Cappio F. The microenvironment in mature B-cell malignancies: a target for new treatment strategies. *Blood*. 2009;114(16):3367-3375.
2. Stevenson FK, Krysov S, Davies AJ, Steele AJ, Packham G. B-cell receptor signaling in chronic lymphocytic leukemia. *Blood*. 2011;118(16):4313-4320.
3. Woyach JA, Johnson AJ, Byrd JC. The B-cell receptor signaling pathway as a therapeutic target in CLL. *Blood*. 2012;120(6):1175-1184.
4. Rushworth SA, Bowles KM, Barrera LN, Murray MY, Zaitseva L, MacEwan DJ. BTK inhibitor ibrutinib is cytotoxic to myeloma and potently enhances bortezomib and lenalidomide activities through NF-κB. *Cell Signal*. 2013;25(1):106-112.
5. 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 USA*. 2010;107(29):13075-13080.
6. 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(1):88-94.
7. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2013;369(1):32-42.
8. 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(1):48-58.

9. Byrd JC, Brown JR, O'Brien S, et al; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med.* 2014;371:213-223.
10. Burger JA, Tedeschi A, Barr PM, et al; RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.
11. Burger JA, Keating MJ, Wierda WG, et al. Safety and activity of ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukaemia: a single-arm, phase 2 study. *Lancet Oncol.* 2014;15(10):1090-1099.
12. Brown JR, Barrientos JC, Barr PM, et al. The Bruton tyrosine kinase inhibitor ibrutinib with chemoimmunotherapy in patients with chronic lymphocytic leukemia. *Blood.* 2015;125(19):2915-2922.
13. Chanan-Khan A, Cramer P, Demirkan F, et al; HELIOS investigators. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. *Lancet Oncol.* 2016;17(2): 200-211.
14. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. *Blood.* 2015;125(16):2497-2506.
15. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2016;374(4): 323-332.
16. Tam C, Griff AP, Opat S, et al. The BTK inhibitor, BGB-311, is safe, tolerable, and highly active in patients with relapsed/refractory B-cell malignancies: initial report of a phase 1 first-in-human trial [abstract]. *Blood.* 2015;126(23). Abstract 832.
17. Fegan C, Bagshaw J, Salles G, et al. A phase I study of the oral BTK inhibitor ONO-4059 in patients with relapsed/refractory and high risk CLL. In: European Hematology Association; 12-15 June 2014; Milan, Italy. Abstract S705.
18. Okkenhaug K, Vanhaesebroeck B. PI3K in lymphocyte development, differentiation and activation. *Nat Rev Immunol.* 2003;3(4):317-330.
19. Herman SE, Gordon AL, Wagner AJ, et al. Phosphatidylinositol 3-kinase-δ inhibitor CAL-101 shows promising preclinical activity in chronic lymphocytic leukemia by antagonizing intrinsic and extrinsic cellular survival signals. *Blood.* 2010;116(12):2078-2088.
20. 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(13):3603-3612.
21. 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(2):591-594.
22. Burger JA, Burger M, Kipps TJ. Chronic lymphocytic leukemia B cells express functional CXCR4 chemokine receptors that mediate spontaneous migration beneath bone marrow stromal cells. *Blood.* 1999;94(11): 3658-3667.
23. Gattei V, Bulian P, Del Principe MI, et al. Relevance of CD49d protein expression as overall survival and progressive disease prognosticator in chronic lymphocytic leukemia. *Blood.* 2008;111(2):865-873.
24. Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110δ, for relapsed/refractory chronic lymphocytic leukemia. *Blood.* 2014;123(22):3390-3397.
25. O'Brien SM, Lamanna N, Kipps TJ, et al. A phase 2 study of idelalisib plus rituximab in treatment-naive older patients with chronic lymphocytic leukemia. *Blood.* 2015;126(25):2686-2694.
26. Barrientos JC, Furman RR, Leonard J, et al. Update on a phase I study of the selective PI3Kδ idelalisib (GS-1101) in combination with rituximab and/or bendamustine in patients with relapsed or refractory CLL [abstract]. *J Clin Oncol.* 2013;31(suppl). Abstract 7017.
27. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2014;370(11):997-1007.
28. Zelenetz AD, Robak T, Coiffier B, et al. Idelalisib plus bendamustine and rituximab (BR) is superior to BR alone in patients with relapsed/refractory chronic lymphocytic leukemia: results of a phase 3 randomized double-blind placebo-controlled study [abstract]. *Blood.* 2015;126(23). Abstract LBA-5.
29. Flinn I, Patel M, Kahl BS, et al. Preliminary safety and efficacy of IPI-145, a potent inhibitor of phosphoinositide-3-kinase-δ,γ, in patients with chronic lymphocytic leukemia [abstract]. *Blood.* 2013; 122(21). Abstract 677.
30. O'Connor OA, Flinn IW, Patel MR, et al. TGR-1202, a novel once daily PI3K-delta inhibitor, demonstrates clinical activity with a favorable safety profile in patients with CLL and B-cell lymphoma [abstract]. *Blood.* 2015;126(23). Abstract 4154.
31. Quiroga MP, Balakrishnan K, Kurtova AV, et al. B-cell antigen receptor signaling enhances chronic lymphocytic leukemia cell migration and survival: specific targeting with a novel spleen tyrosine kinase inhibitor, R406. *Blood.* 2009;114(5):1029-1037.
32. Buchner M, Baer C, Prinz G, et al. Spleen tyrosine kinase inhibition prevents chemokine- and integrin-mediated stromal protective effects in chronic lymphocytic leukemia. *Blood.* 2010;115(22):4497-4506.
33. Friedberg JW, Sharman J, Sweetenham J, et al. Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia. *Blood.* 2010;115(13):2578-2585.
34. Braselmann S, Taylor V, Zhao H, et al. R406, an orally available spleen tyrosine kinase inhibitor blocks fc receptor signaling and reduces immune complex-mediated inflammation. *J Pharmacol Exp Ther.* 2006;319(3): 998-1008.
35. Sharman JP, Klein L, Boxer M, et al. Phase 2 trial of GS-9973, a selective Syk inhibitor, in chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) [abstract]. *Blood.* 2013;122(21). Abstract 1634.
36. Barr PM, Saylors GB, Spurgeon SE, et al. Phase 2 study of idelalisib and entospletinib: pneumonitis limits combination therapy in relapsed refractory CLL and NHL. *Blood.* 2016;127(20):2411-2415.
37. Danial NN, Korsmeyer SJ. Cell death: critical control points. *Cell.* 2004; 116(2):205-219.
38. Strasser A, Huang DC, Vaux DL. The role of the bcl-2/ced-9 gene family in cancer and general implications of defects in cell death control for tumourigenesis and resistance to chemotherapy. *Biochim Biophys Acta.* 1997;1333(2):F151-F178.
39. Schmitt CA, Lowe SW. Bcl-2 mediates chemoresistance in matched pairs of primary E(mu)-myc lymphomas in vivo. *Blood Cells Mol Dis.* 2001; 27(1):206-216.
40. Kitada S, Takayama S, De Riel K, Tanaka S, Reed JC. Reversal of chemoresistance of lymphoma cells by antisense-mediated reduction of bcl-2 gene expression. *Antisense Res Dev.* 1994;4(2):71-79.
41. Roberts AW, Seymour JF, Brown JR, et al. Substantial susceptibility of chronic lymphocytic leukemia to BCL2 inhibition: results of a phase I study of navitoclax in patients with relapsed or refractory disease. *J Clin Oncol.* 2012;30(5):488-496.
42. Roberts AW, Davids MS, Pagel JM. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2016;374(4): 311-322.
43. Ma S, Brander DM, Seymour JF, et al. Deep and durable responses following venetoclax (ABT-199/GDC-0199) combined with rituximab in patients with relapsed/refractory chronic lymphocytic leukemia: results from a phase 1b study [abstract]. *Blood.* 2015;126(23). Abstract 830.
44. Fischer K, Fink AM, Bishop H, et al. Results of the Safety Run-In Phase of CLL14 (BO25323): a prospective, open-label, multicenter randomized phase-III trial to compare the efficacy and safety of obinutuzumab and venetoclax (GDC-0199/ABT-199) with obinutuzumab and chlorambucil in patients with previously untreated CLL and coexisting medical conditions [abstract]. *Blood.* 2015;126(23). Abstract 496.
45. Flinn IW, Brunvand M, Choi MY, et al. Safety and efficacy from a combination of venetoclax (GDC-0199/ABT-199) and obinutuzumab in patients with relapsed/refractory or previously untreated chronic lymphocytic leukemia: results from an ongoing phase Ib study (GP28331) [abstract]. *Blood.* 2015;126(23). Abstract 494.
46. Jones J, Mato AR, Coutre S, et al. Preliminary results of a phase 2, open-label study of venetoclax (ABT-199/GDC-0199) monotherapy in patients with chronic lymphocytic leukemia relapsed after or refractory to ibrutinib or idelalisib therapy [abstract]. *Blood.* 2015;126(23). Abstract 715.

47. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax (ABT-199/GDC-0199) monotherapy induces deep remissions, including complete remission and undetectable MRD, in ultra-high risk relapsed/refractory chronic lymphocytic leukemia with 17p deletion: results of the Pivotal International Phase 2 Study [abstract]. *Blood*. 2015;126(23). Abstract LBA-6.
48. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med*. 2014; 370(12):1101-1110.
49. Hillmen P, Robak T, Janssens A, et al; COMPLEMENT 1 Study Investigators. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. *Lancet*. 2015;385(9980):1873-1883.
50. Brentjens RJ, Rivière I, Park JH, et al. Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias. *Blood*. 2011; 118(18):4817-4828.
51. Brentjens RJ, Davila ML, Riviere I, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. *Sci Transl Med*. 2013;5(177):177ra38.
52. Porter DL, Levine BL, Kalos M, et al. Randomized, phase II dose optimization study of chimeric antigen receptor modified T cells against CD19 (CTL019) in patients with relapsed refractory CLL [abstract]. *Blood*. 2013;122(21). Abstract 873.
53. Ding W, Cong H, Call T, et al. PD-1 blockade with pembrolizumab (MK-3475) in relapsed/refractory CLL including Richter transformation: an early efficacy report from a phase 2 trial (MC1485) [abstract]. *Blood*. 2015;126(23). Abstract 834.
54. Beckwith KA, Frissora FW, Stefanovski MR, et al. The CD37-targeted antibody-drug conjugate IMGN529 is highly active against human CLL and in a novel CD37 transgenic murine leukemia model. *Leukemia*. 2014; 28(7):1501-1510.
55. Topp MS, Gökbuget N, Zugmaier G, et al. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. *J Clin Oncol*. 2014; 32(36):4134-4140.
56. Goebeler ME, Knop S, Viardot A, et al. Bispecific T-cell engager (BiTE) antibody construct blinatumomab for the treatment of patients with relapsed/refractory non-Hodgkin lymphoma: final results from a phase I study. *J Clin Oncol*. 2016;34(10):1104-1111.