BCL-2 As a Therapeutic Target in Chronic Lymphocytic Leukemia

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Abstract: Venetoclax (formerly ABT-199) was recently approved in the United States for the treatment of patients who have relapsed or refractory chronic lymphocytic leukemia (CLL) with the 17p deletion. Venetoclax has demonstrated marked activity as monotherapy as well as in combination with cytotoxic chemotherapies, B-cell receptor inhibitors, and anti-CD20 monoclonal antibodies across the spectrum of CLL. The potency of venetoclax has been associated with a unique ability to induce deep (minimal residual disease–negative) complete remissions that appear to be durable. Its toxicity profile includes manageable hematologic toxicities, as well as the potential for tumor lysis syndrome. Here, we review the BCL-2 pathway and the mechanism of action of BCL-2 inhibitors, the activity and safety profile of venetoclax, and the practical application of venetoclax in the management of patients with CLL.

Keywords
B-cell lymphoma 2 protein, chronic lymphocytic leukemia, minimal residual disease, venetoclax

Introduction

The last decade has seen significant advancements in the management of chronic lymphocytic leukemia (CLL). Most notable has been the integration of small-molecule inhibitors of the B-cell receptor pathway—ibrutinib (Imbruvica, Pharmacyclics/Janssen) and idelalisib (Zydelig, Gilead)—into common practice. Ibrutinib and idelalisib have been shown to be effective in the frontline and relapsed/refractory settings as well as in patients with high-risk clinical and genetic prognostic factors; consequently, both agents have been approved by the US Food and Drug Administration (FDA).

The FDA recently approved another orally available small-molecule inhibitor, venetoclax (Venclexta, AbbVie/Genentech), which works through inhibition of a protein in the B-cell lymphoma (BCL) family. By binding the antiapoptotic protein BCL-2, venetoclax induces apoptosis in CLL cells.

In this review, we discuss the BCL-2 pathway, the mechanism of action of BCL-2 inhibitors, and the available preclinical and clinical data for venetoclax. Additionally, we discuss the clinical use of this drug and the management of its most significant toxicities when it is used as monotherapy or in novel combinations.

Table 1. Key Proteins in the BCL-2 Pathway

	Antiapoptotic	Proapoptotic		
	BCL-2 Proteins	***Sensitizers***	***Activators***	***Cell Death Mediators***
Members	BCL-2, BCL-XL, MCL-1	BAD, BIK, NOXA, BMF, HRK, PUMA	BID, BIM	BAX, BAK
BCL-2 homology domains	BH1, BH2, BH3, BH4	BH3 only	BH3 only	BH1, BH2, BH3
Function in normal B cell	Sequester sensitizers and activators, preventing oligomerization of cell death mediators; interact with cell death mediators, preventing oligomerization.	Sensitizers bind BH3 binding cleft on BCL-2, freeing activators to induce oligomerization of cell death mediators.	Activators induce allosteric changes that result in oligomerization of BAX and BAK.	Oligomerization leads to MOMP, inducing caspase-dependent apoptosis.
Function in CLL	BCL-2 is upregulated, preventing apoptosis.	BH3 mimetics (venetoclax) act as sensitizers, freeing BIM to induce apoptosis.	BIM is overexpressed but constitutively bound to BCL-2.	Oligomerization leads to MOMP, inducing caspase-dependent apoptosis only when BCL-2 is blocked.

BCL-2, B-cell lymphoma 2; BCL-XL, B-cell lymphoma extra large; CLL, chronic lymphocytic leukemia; MCL-1, myeloid cell leukemia 1; MOMP, mitochondrial outer membrane permeabilization.

The BCL-2 Pathway

The proteins of the BCL-2 family are important regulators of apoptosis that are mediated by the caspase-dependent mitochondrial pathway.[1,2] CLL cells are particularly dependent on inhibition of this pathway for survival,[3] so interference in BCL-2 signaling serves as a promising target for CLL therapy.

The proteins of the BCL-2 family exist as both proapoptotic and antiapoptotic subtypes, each of which contains one or more of the BCL-2 homology domains: BH1, BH2, BH3, and BH4 (Table 1).[1]

The proapoptotic proteins can be subdivided into 3 groups: sensitizers, activators, and cell death mediators. In a healthy cell, antiapoptotic proteins sequester both sensitizers and activators. When the cell is stressed, death signals release both sensitizers and activators. The activators bind the BAX family proteins (BAX and BAK), leading to their oligomerization.[4-7] The oligomerization of BAX and BAK leads to mitochondrial outer membrane permeabilization (MOMP), which results in the release of cytochrome C and other apoptotic factors and ultimately in caspase-mediated cell death.[8,9] The sensitizers themselves are not capable of inducing BAX/BAK oligomerization; instead, they serve to counteract the role of the antiapoptotic proteins by binding the antiapoptotic BCL-2 proteins.[7,10,11]

BCL-2 proteins prevent cell death by binding and sequestering the activators in their BH3 homology cleft, thereby preventing the activators from inducing the oligomerization of BAX/BAK.[12] The sensitizers antagonize this action by binding the antiapoptotic BCL-2 proteins, freeing the activators to induce BAX/BAK oligomerization. Importantly, although BCL-2 seems to be the primary antiapoptotic BCL protein in B cells, BCL extra large (BCL-XL) is expressed in platelets, promoting programmed cell death in aging platelets.[13,14] BCL-2 proteins, including BCL-2 and BCL-XL, also directly interact with the cell death mediators BAX and BAK, preventing their oligomerization and the initiation of MOMP.[15,16]

BCL-2 and Chronic Lymphocytic Leukemia

The homeostasis of proapoptotic and antiapoptotic factors is fundamentally different in the CLL cell than in the normal B cell. The CLL cell exists in a constant state of stress, and therefore the activators—most specifically BIM—are expressed at high levels, in contrast to their quiescent state in the normal B cell.[3] To offset this activation and prevent apoptosis, CLL cells upregulate BCL-2, resulting in the sequestration of BIM. Therefore, in a model initially described by Letai and colleagues, CLL cells exist in a state in which they are primed for cell death.[3,17] BCL-2 inhibitors induce apoptosis in CLL cells by acting as sensitizers. They are BH3 mimetics that bind

the BH3 binding site on the BCL-2 protein, freeing BIM to induce the oligomerization of BAX/BAK and resulting in apoptosis.

Targeting BCL-2

ABT-737

With an understanding of the role of BCL-2 in apoptosis, Oltersdorf and colleagues deliberately developed the first small-molecule BH3 mimetic, ABT-737, via high-throughput nuclear magnetic resonance–based screening, parallel synthesis, and structure-based design.[18] ABT-737 binds with high affinity to the BH3-binding domain of BCL-2, BCL-XL, and BCL-W (but not myeloid cell leukemia 1 [MCL-1]), functioning similarly to the sensitizer BH3-only proteins (ie, it does not directly induce oligomerization of BAX and BAK, but rather frees BIM for this purpose). Supporting the model in which the sensitizers function to free activators to induce apoptosis in the setting of cellular stress, ABT-737 displays synergism with chemotherapeutics and radiation, allowing decreased doses of each for cytotoxic effects in the presence of ABT-737.[18] Indicating its particular affinity for the "primed for death" CLL cells, ABT-737 demonstrated concentration-dependent apoptosis in 13 of 15 patient-derived CLL B-cell specimens in vitro.[18] In addition to killing CLL cells and other solid-tumor cells in vitro, ABT-737 induced apoptosis in platelets in vivo, likely owing to its affinity for the platelet-specific BCL-XL.[13]

Navitoclax (ABT-263)

Despite its affinity for BCL-2 and its ability to induce apoptosis in CLL cells in vitro, ABT-737 possesses poor therapeutic potential given its lack of oral bioavailability and its low aqueous solubility (which makes intravenous delivery difficult as well). Thus, a second-generation BCL-2 inhibitor with oral bioavailability, navitoclax (ABT-263), was developed by using targeted modifications of 3 key positions on ABT-737.[19] Like ABT-737, navitoclax binds BCL-XL, BCL-2, and BCL-W with high affinity. Preclinical data demonstrated that navitoclax induces a rapid and reversible thrombocytopenia, even after a single dose, likely owing to its high affinity for BCL-XL.[20]

Two phase 1 clinical trials evaluated the safety and efficacy of navitoclax as a single agent in patients with CLL. The first, published in 2010 by Wilson and colleagues, included 55 patients, 20 of them with CLL/small lymphocytic leukemia. Those with CLL demonstrated the greatest clinical response, with a mean progression-free survival (PFS) of 246 days. The most common serious toxic effects included grade 3 or 4 thrombocytopenia (in 29 patients), grade 3 or 4 lymphocytopenia (in 18 patients), and grade 3 or 4 neutropenia (in 18 patients).[21] A second phase 1 trial, published by Roberts and colleagues in 2012, included 29 patients with relapsed or refractory CLL and demonstrated similar efficacy, with a median PFS of 25 months. This response was observed in patients with attributes typical of refractory disease, including refractoriness to fludarabine, bulky adenopathy, and the 17p deletion. Once again, thrombocytopenia remained the major dose-limiting toxicity.[22]

Venetoclax (ABT-199)

Given the clinically significant thrombocytopenia associated with navitoclax, Souers and colleagues employed a rational drug design strategy based on a co-crystal structure to develop venetoclax, a selective BCL-2 inhibitor that spares BCL-XL binding.[23] Preclinical work demonstrated that the binding affinity of this compound for BCL-XL is 3 orders of magnitude lower than its binding affinity for BCL-2. In both ex vivo and in vivo murine models, venetoclax failed to induce significant thrombocytopenia. Venetoclax induced apoptosis in vitro in 15 human CLL cell specimens.[23]

The first study of venetoclax in humans began with 3 patients who had refractory CLL, each of whom received a single dose of venetoclax. All 3 patients demonstrated a marked reduction in palpable lymphadenopathy within 24 hours of their dose, and the 2 patients with pretreatment lymphocytosis demonstrated a significant reduction in lymphocytosis. All patients demonstrated laboratory evidence of tumor lysis, including elevated serum lactate dehydrogenase (LDH) and phosphate levels. Platelet reductions due to venetoclax were not clinically significant in these 3 patients.[23]

Subsequent phase 1 and phase 2 clinical trials demonstrated that single-agent venetoclax is a potent antileukemic therapy in patients with CLL.[24-26] Table 2 summarizes the early-phase clinical trials of venetoclax as monotherapy in patients with CLL. In April of 2016, venetoclax was granted approval for the treatment of patients who have CLL with the 17p deletion, detected by an FDA-approved test, and have received at least 1 prior therapy.[27]

Clinical Data: Venetoclax As Monotherapy

Venetoclax appears to be highly effective and capable of inducing deep remissions in patients with relapsed or refractory CLL, including those with poor genetic and clinical prognostic factors and those whose disease has failed to respond to targeted B-cell receptor therapy with ibrutinib or idelalisib. In the 2 published clinical trials evaluating venetoclax monotherapy (Roberts and colleagues[24]

Table 2. Summary of Clinical Trials of Venetoclax As Monotherapy in CLL

Authors	Intervention	Trial Type	Patient Population	Patients	Time to First Response; Time to CR	ORR; CR Rate	Duration of PFS	Bone Marrow MRD	Grade 3/4 Toxicities (≥5%)	Incidence of TLS (Laboratory; Clinical)
Roberts et al[24]	Venetoclax monotherapy	Phase 1 dose-escalation trial with expansion cohort; single-arm	R/R CLL/SLL; 89% with resistance to fludarabine, del(17p), unmutated *IGHV* gene, or bulky adenopathy	116 dose escalation	6 wk; 6 mo	79%; 20%	25 mo	6 (5%)	Neutropenia (41%), anemia 12%), thrombocytopenia (12%), hyperglycemia (9%)	9%; 3% (no clinical TLS after dose ramp-up introduced)
Stilgenbauer et al[25]	Venetoclax monotherapy	Phase 2; single-arm	R/R CLL; del(17p)	107	3.2 wk; 8.2 mo	79%; 10%	NR	6 (5%) ; peripheral MRD negativity achieved in 18 patients	Neutropenia (40%), anemia (18%), infection (19%), thrombocytopenia (15%), AIHA (7%), ITP (5%), leukopenia (5%), TLS (5%)	5%; 0%
Jones et al[26]	Venetoclax monotherapy	Phase 2; preliminary results	CLL relapsed after or refractory to ibrutinib or idelalisib	64 (43 after ibrutinib, 21 after idelalisib)	NA	Ibrutinib patients, 67%-70%; idelalisib patients, 48%-57%	NR	Not assessed; peripheral MRD negativity achieved in 14 of 43 patients (33%)	Neutropenia (31%), anemia (22%), thrombocytopenia (16%)	3%; 0%

AIHA, autoimmune hemolytic anemia; CLL, chronic lymphocytic leukemia; CR, complete remission; IGHV, immunoglobulin heavy chain variable region; ITP, immune thrombocytopenia; mo, months; MRD, minimal residual disease; NA, not available; NR, not reached; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed or refractory; SLL, small lymphocytic leukemia; TLS, tumor lysis syndrome; wk, weeks.

and Stilgenbauer and colleagues[25]), the overall response rates were high (79% in both studies) in patients with high rates of negative prognostic factors, including resistance to fludarabine, chromosome 17p deletion, unmutated immunoglobulin heavy chain variable region gene (*IGHV*), and bulky adenopathy. Further, a deep remission was achieved in a substantial percentage of patients, including a fraction of patients with a complete remission (20% and 10%, respectively). Preliminary results of a study of venetoclax monotherapy in patients with CLL whose disease had relapsed after or progressed during treatment with either ibrutinib or idelalisib indicate that venetoclax is also safe and effective in this population with highly refractory disease.[28] An overall response rate of 67% to 70% was demonstrated at 24 weeks in 39 patients on venetoclax and previously treated with ibrutinib. Similarly, an overall response rate of 48% to 57% was achieved in 21 patients previously treated with idelalisib and then treated with venetoclax during this same period. Thus, venetoclax demonstrates activity and durable responses in patients with negative clinical prognostic factors, those with negative genetic prognostic factors, and those whose disease has failed to respond to therapy targeting the B-cell receptor pathway. All these populations of patients have an extremely poor prognosis.

Importantly, although a first objective response is seen early in therapy (at between 3 and 6 weeks in all studies), in both published studies, responses continued to be achieved and maintained after extended periods. For example, Roberts and colleagues reported that 3 patients first achieved a complete remission after more than 12 months of therapy. In both studies, the median duration of overall PFS was not reached, but in the study of Roberts and colleagues, the median duration of PFS in the initial dose-escalation cohort was 25 months.

Additionally, early data suggest that patients whose disease failed to respond to venetoclax (ie, all patients who

discontinued venetoclax for reasons other than voluntary drug hold following achievement of complete remission) had significantly better overall survival (OS) than that previously reported in patients whose disease progressed following ibrutinib or idelalisib therapy. In 2 retrospective studies, median PFS following ibrutinib discontinuation in patients with CLL progression or Richter's transformation was reported to be 8 months and 6 months; OS was reported to be 17.6 months and 3.5 months.[29,30] A similar retrospective study in patients whose disease failed to respond to venetoclax reported that at a median follow-up of 12.5 months, median PFS in patients with progression had not been reached (12-month OS, 69%) and was 12 months in patients with Richter's transformation.[31] Therefore, the prognosis of patients with progression following venetoclax may be better than the prognosis of patients with progression on agents that target the B-cell receptor. These data suggest that further studies of strategies for sequencing novel agents are warranted.

Toxicities

The most common grade 3 or 4 toxicity in all studies was neutropenia, present in 31% to 40% of patients. Other serious toxicities, which are summarized in Table 2, included other cytopenias (eg, anemia, thrombocytopenia, and leukopenia). Patients on therapy also experienced grade 3 or 4 autoimmune cytopenias, including immune thrombocytopenic purpura (3%-5% of patients) and autoimmune hemolytic anemia (7% of patients in the study of Stilgenbauer and colleagues; not reported in the study of Roberts and colleagues).

In addition to the cytopenias previously noted, common grade 1 or 2 toxicities included fatigue (22%-40%), upper respiratory infection (15%-48%), and gastrointestinal disorders—specifically diarrhea (29%-52%), nausea (28%-47%), constipation (10%-21%), and vomiting (14%-21%).

Management of Neutropenia

Neutropenia remains an important, clinically significant toxicity associated with venetoclax treatment. Neutropenia also developed in patients treated with navitoclax, suggesting that this is a class effect associated with BCL-2 inhibition.[21,22] Despite the relatively high rates of neutropenia, the rates of infections associated with neutropenia (4.7% and 6% of all patients) were lower than those previously described in patients with CLL receiving cytotoxic chemotherapy. Of note, no antibiotic prophylaxis was mandated in these studies.

Neutropenia was managed conservatively in both the phase 1 and phase 2 clinical trials, with the administration of granulocyte colony-stimulating factor (G-CSF) in most patients and rarely with dose reductions or interruptions (<10% of the total number of patients in each study). No patients in either study permanently discontinued venetoclax owing to neutropenia.[24,25]

Based on experience in the clinical trials, the recommended management of neutropenia in the FDA package insert for venetoclax includes the administration of G-CSF as clinically indicated and dose interruption in the setting of neutropenia with infection or fever. In the absence of infection, dose interruption is recommended in cases of grade 4 neutropenia (an absolute neutrophil count $<500/mm^3$). In the setting of a first neutropenic infection, venetoclax should be resumed at the same dose given before the interruption. Dose reduction is recommended in the setting of recurrent neutropenic infections.

Management of Tumor Lysis Syndrome

In patients in the early phase 1 studies, tumor lysis syndrome (TLS) was the most clinically significant toxicity. As previously noted, the first human study with this drug involved administration to 3 patients with refractory CLL, all of whom exhibited tumor lysis after a single dose of venetoclax, with marked elevation of LDH and phosphate.[23] In the dose-escalation cohort of the phase 1 trial of venetoclax in CLL, 10 of 56 patients (18%) demonstrated laboratory evidence of tumor lysis, which was clinically significant in 3 cases. In all patients (11 episodes in 10 patients), TLS occurred either following a first dose of 200 mg (2 patients), 100 mg (1 patient), or 50 mg (4 patients), or following administration of the ramp-up dose of 150 mg (2 patients), 800 mg (1 patients), and 1200 mg (1 patient). Tumor lysis generally did not recur in those in whom it developed; following the resolution of tumor lysis, 9 of the 10 patients resumed venetoclax, and tumor lysis did not recur in 8 of them.

In 2 of the 3 patients with clinically significant tumor lysis, the sequelae were severe: acute renal failure requiring dialysis and a 24-day hospitalization (after an initial 50-mg dose) in 1 patient and sudden death (after a ramp-up dose to 1200 mg) in 1 patient.

Following the significant tumor lysis in these early patients, Roberts and colleagues developed a dose-escalation and monitoring protocol to avoid toxicities associated with tumor lysis. This protocol has been used in all subsequent clinical trials and is also included in the dosing instructions in the venetoclax package insert. Per this protocol, patients complete a 4-week ramp-up regimen before reaching the target dose at week 5 (20 mg daily for 7 days, then 50 mg daily for 7 days, then 100 mg daily for 7 days, and finally 200 mg daily for 7 days). After 4 weeks, the target dose of 400 mg daily is reached.

The degree of tumor lysis prophylaxis and monitoring is determined on the basis of the patient's risk for

tumor lysis, indicated by the amount of bulky lymphadenopathy and level of peripheral lymphocytosis. Those at high risk for TLS (any lymph node >10 cm, or any lymph node >5 cm with an absolute lymphocyte count >25,000/μL) are treated with allopurinol and oral and intravenous hydration, and they are monitored in the inpatient setting for their initial 20- and 50-mg doses at a minimum. For patients at high risk for tumor lysis with an elevated baseline uric acid level, rasburicase for tumor lysis prevention should be considered. With this ramp-up and prophylaxis protocol, the risk for clinically significant TLS has been substantially decreased. In subsequent trials using this protocol, 3% to 5% of patients had laboratory TLS, and no clinical TLS was reported.[25-27]

Importantly, venetoclax is metabolized by cytochrome P-450 3A (CYP3A), and strong inhibitors of CYP3A are contraindicated in the initiation and ramp-up dosing phases owing to the increased risk for tumor lysis. Following the ramp-up phase, these inhibitors should still be avoided if possible. If not, venetoclax dosing should be reduced by 75%. Moderate CYP3A and P-glycoprotein inhibitors should be avoided in all phases, but if this is not possible, venetoclax dosing should be reduced by at least 50%. We recommend pharmacy consultation for all patients starting venetoclax therapy to determine possible interactions with concomitant medications and appropriate dosing.

Combination Therapy

Although venetoclax demonstrates promising efficacy as monotherapy, active investigation is also under way in phase 1 and phase 2 clinical trials to determine whether it may have additive or synergistic efficacy when used in combination with either anti-CD20 antibodies or small-molecule inhibitors of the B-cell receptor pathway.

Combination With Monoclonal Antibodies

Both preclinical and clinical data suggest that the efficacy of venetoclax may be increased when it is combined with the anti-CD20 antibodies. In a CLL model with CD40-induced venetoclax resistance, treatment with anti-CD20 antibodies, including rituximab (Rituxan, Genentech/Biogen Idec) and obinutuzumab (Gazyva, Genentech), counteracted ABT-199 resistance.[32] In a BCL xenograft mouse model that was inherently resistant to navitoclax, navitoclax demonstrated synergistic activity with rituximab.[20]

Preliminary data from 4 clinical trials looking at venetoclax in combination with anti-CD20 antibodies—the chimeric mouse/human antibody rituximab and the humanized antibody obinutuzumab—have been published to date. The major findings from these trials are summarized in Table 3. Although all 4 trials remain active, early reported data suggest that this combination is promising, with high overall response rates, high rates of complete remission/complete remission with incomplete blood count recovery, high rates of minimal residual disease (MRD)–negative status, and a tolerable side effect profile, similar to that seen with venetoclax monotherapy.

In addition to the trials previously mentioned, 2 other trials studying venetoclax in combination with anti-CD20 antibodies and the alkylating agent bendamustine (Treanda, Teva) are currently active. These include an analysis of venetoclax in combination with bendamustine/rituximab vs venetoclax in combination with bendamustine/obinutuzumab (NCT01671904)[33] and a sequential regimen of bendamustine debulking followed by venetoclax/obinutuzumab induction and maintenance (NCT02401503).[34]

Combination With Small Molecules

Preclinical data also suggest that the potency of venetoclax may be increased when it is combined with a B-cell receptor signaling inhibitor, such as ibrutinib or idelalisib. In vitro studies of human CLL cells demonstrated synergistic improvement in apoptosis in 5 of 9 CLL samples treated with the combination of ibrutinib and venetoclax vs a single agent.[35] Serial ex vivo sampling of cells from patients with CLL currently being treated with ibrutinib that were exposed to ABT-199 in vitro demonstrated high rates of cell death.[36] Similarly, synergistic levels of apoptosis were observed in vivo with the combination of venetoclax plus idelalisib or entospletinib (a small-molecule spleen tyrosine kinase inhibitor).[37] Deng and colleagues suggest that the mechanism of this synergism is an increased mitochondrial dependence on BCL-2 to avoid apoptosis in cells pretreated with ibrutinib,[38] whereas Jayappa and colleagues suggest that signaling through CD40, interleukin 1 (IL-1), and Toll-like receptors (TLRs) leads to increased nuclear factor κB (NF-κB), JAK/STAT, or phosphoinositide 3-kinase (PI3K) signaling.[39] A phase 2 clinical trial studying venetoclax and ibrutinib combination therapy in patients with relapsed or refractory CLL or in patients with previously untreated CLL and high-risk features is currently under way (NCT02756897).[40]

Venetoclax, B-Cell Receptor Signaling, and Anti-CD20 Combination Therapy

Multiple clinical trials are also evaluating the efficacy of venetoclax in combination with both ibrutinib and anti-CD20 antibodies in the hope that an even greater synergistic effect will be achieved. These include a phase 1b/2 clinical trial evaluating the safety and efficacy of venetoclax/obinutuzumab/ibrutinib in patients with relapsed, refractory, or previously untreated CLL

Table 3. Summary of Clinical Trials of Venetoclax and Anti-CD20 Therapy Currently in Progress

Authors	Intervention	Trial Phase	Characteristics of Patient Population	No. of Patients	Outcome	MRD Negativity	Toxicities
Stilgenbauer et al[49]	Venetoclax + bendamustine/rituximab or bendamustine/obinutuzumab	Phase 1b	R/R and first-line therapy	55 total; 47 Ven+BR (30 R/R, 17 FL); 8 Ven+BG (8 FL)	100% ORR in 20 R/R patients; 3/20 with CRi	VEN + BR in R/R 16/21 (76%); Ven + BR in FL 6/9 (67%); VEN + BG 2/4; MRD not assessed in all enrolled patients at time of reporting	Neutropenia (61%), nausea (56%), thrombocytopenia (52%), diarrhea (38%), fatigue (25%)
Seymour et al[48]	Venetoclax + rituximab	Phase 1b	R/R	49	86% ORR, 82% PFS at 24 mo; 51% with CRi	28/49 (57%); 20/25 with CR/CRi (80%)	Infections (81%), neutropenia (55%), diarrhea (57%), upper respiratory infection (45%), fatigue (37%), pyrexia (39%), cough (35%), headache (33%), thrombocytopenia (21%)
Fischer et al[50]	Venetoclax + obinutuzumab vs chlorambucil + obinutuzumab	Phase 3 (only safety run-in phase reported thus far)	Untreated CLL and coexisting medical conditions	12	100% ORR; 58% CR/CR;	83% with no peripheral MRD	Infusion reaction (75%), neutropenia (66.7%), diarrhea (50%), hyperkalemia (41.7%), infection (66.7%)
Flinn et al[51]	Venetoclax + obinutuzumab	Phase 1b	R/R and first-line therapy	32 (26 R/R, 6 FL); 17 patients with response evaluation at the time of reporting	17/17 (100%) ORR ; 4/17 (23.5%) CR/CRi	"Some patients may have achieved MRD-negative status by cycle 4"	Infection (50%), diarrhea (50%), infusion reaction (40.6%), nausea (37.5%), neutropenia (37.5%), fatigue (31.1%), hypophosphatemia (31.1%)

CLL, chronic lymphocytic leukemia; CR, complete remission; CRi, complete remission with incomplete blood count recovery; MRD, minimal residual disease; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed or refractory.

(NCT02427451),[41] as well as a multiple-arm phase 3 randomized trial comparing standard chemotherapy with fludarabine/cyclophosphamide/rituximab (FCR) or bendamustine/rituximab vs rituximab/venetoclax vs obinutuzumab/venetoclax vs obinutuzumab/ibrutinib/venetoclax in patients who have previously untreated CLL without 17p deletions or *TP53* mutations (NCT02950051).[42]

Minimal Residual Disease As an Endpoint

MRD negativity (ie, the absence of detectable CLL cells on tests using highly sensitive flow cytometric and molecular techniques) following CLL-directed therapy has been shown in multiple settings to predict favorable outcomes independently in patients with CLL, including improved PFS and OS, in comparison with failure to achieve MRD negativity.[43-47] However, MRD negativity is important not only as a prognostic factor; it may also be an important treatment endpoint. Among patients treated with FCR in the frontline setting, MRD-negative patients who discontinued therapy early (after 3 cycles) had PFS and OS similar to those of patients who completed additional courses of FCR and also achieved MRD negativity.[45]

Venetoclax, both as monotherapy and in combination, appears capable of inducing deep and sustained remissions, demonstrated by the achievement of MRD negativity. The rates of MRD negativity reported in various clinical trials are summarized in Tables 2 and 3. These include particularly high rates of bone marrow MRD-negative status in patients receiving venetoclax and rituximab combination therapy in the setting of relapsed or refractory disease (as high as 57% of all patients in the study).[48] This finding raises the possibility of a time-limited approach to venetoclax therapy, with MRD negativity used as an endpoint for treatment cessation.

Conclusions

Venetoclax, a highly selective inhibitor of the antiapoptotic BCL-2 protein, was developed via rational drug design with the use of high-throughput nuclear magnetic resonance–based screening and structure-based design. This small molecule induces apoptosis by binding BCL-2, freeing proapoptotic proteins to activate the caspase-dependent MOMP pathway. Owing to their dependence on BCL-2 for survival, CLL cells are particularly susceptible to cell death via this mechanism. In clinical trials, venetoclax consistently has been shown to be highly effective in patients with CLL both as monotherapy and in combination with anti-CD20 monoclonal antibodies and small-molecule B-cell receptor pathway inhibitors. Venetoclax appears capable of inducing deep and sustained remissions, measured by the absence of MRD in patients treated with this drug. Further studies are required to determine if MRD can be used as an endpoint for therapy, to allow time-limited CLL-directed therapy.

Disclosures

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