

The expanding role of venetoclax in chronic lymphocytic leukemia and small lymphocytic lymphoma

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Abstract: The BCL-2 protein family members inhibit cellular apoptosis, and their overexpression represents a common survival adaptation in cancer. Recently, a selective BCL-2 inhibitor ABT-199, venetoclax, has demonstrated remarkable activity in relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), both as a single agent and in combination with anti-CD20 immunotherapies, such as rituximab. In this article, we review the development and latest clinical data that have led to the expanded approval of venetoclax with rituximab in relapsed/refractory CLL/SLL. We also discuss ongoing and future clinical trials designed to evaluate the efficacy of venetoclax in previously untreated patients and to investigate venetoclax combinations with inhibitors of B-cell receptor signaling pathway. These studies hope to offer an expanded list of chemotherapy-free regimens for patients with CLL/SLL.

Keywords: CLL, SLL, venetoclax, BCL2

Introduction

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a B-cell lymphoproliferative disorder and the most common form of leukemia in adults.¹ Diagnosis of CLL requires the presence of greater than $5 \times 10^9/L$ peripheral blood (PB) monoclonal B-lymphocytes for 3 months as demonstrated by light chain restriction on flow cytometry, whereas SLL is characterized by lymphadenopathy or organomegaly with diagnosis often established by histopathological evaluation of a lymph node or tissue biopsy.² CLL/SLL is differentiated from other B-cell non-Hodgkin lymphomas by a characteristic immunophenotype (CD5+, CD23+, CD19+, dim CD20+) on flow cytometry or immunohistochemistry staining.³ CLL/SLL with adverse prognostic features, such as an unmutated immunoglobulin heavy-chain variable region (IGHV),⁴ presence of a *TP53* mutation or deletions in chromosome 17p (del(17p)),⁵ deletion of 11q,⁶ and expression of ZAP70 (>20%)⁷ or CD38 (>30%),⁸ are associated with more aggressive disease course. Most patients with CLL/SLL are diagnosed at an early asymptomatic stage that can be monitored with expectant observation. Treatment is reserved for symptomatic patients, progressive cytopenias, bulky and progressive lymphadenopathy and/or splenomegaly, and related autoimmune cytopenias not responsive to immunosuppressive therapy alone.⁹

The median age of CLL diagnosis is 72 years of age.⁹ Many CLL patients have significant comorbid conditions and therefore may not be good candidates for conventional immunochemotherapies due to the concerns for both short- and long-term toxicities.

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Novel therapies with enhanced efficacy and improved toxicity profiles are therefore highly desired. To this end, the past three decades have seen substantial progress in the management of CLL/SLL utilizing anti-CD20 immunotherapy and molecular inhibitors of B-cell proliferation and survival. This review focuses on one of the most promising molecular inhibitors, venetoclax, and its expanding use in CLL/SLL.

BCL-2 inhibition with venetoclax in CLL/SLL

Cancer cells hijack a number of cellular processes to gain proliferative and survival advantages. One example is inhibition of apoptosis, the intrinsic cell death program in eukaryotic cells. The pro-survival BCL-2-like protein family, which includes BCL-2 itself, BCL-X_L, BCL-W, and MCL-1, among others, interact with BH3 containing pro-apoptotic proteins, such as BAX and BAK, with different specificities to inhibit apoptosis.^{10,11} Cancer cells overexpress pro-survival BCL-2-like proteins providing resistance against genotoxic stress, radiation, and chemotherapy. Chromosomal 18 abnormalities, the site of the BCL-2 locus, are common in a variety of non-Hodgkin lymphomas (such as t(14:18) in follicular lymphoma) but are observed infrequently in CLL/SLL.¹² However, other mechanisms lead to BCL-2 overexpression in CLL/SLL, including heightened BCL2 translation secondary to loss of miR-15/16 inhibition.^{13,14} miR-15/16 is located on chromosome 13, the location of the most frequently detected chromosomal abnormality (13q14.3) in patients with CLL/SLL.¹⁵ BCL-2 inhibition to directly target the apoptosis machinery was thus explored as a therapeutic strategy in CLL/SLL.

Initial strategies to interrupt BCL-2 pro-survival signaling focused on the pan-BCL2 family inhibitors ABT-263 (navitoclax) and GX015-070 (obatoclax).^{16,17} These agents are classified as BH3-mimetics, designed to bind and inhibit the antiapoptotic BCL-2-like proteins (including BCL-2 and BCL-X_L) and allow apoptosis to proceed in a BAX/BAK-dependent manner. Both of these agents are active in patients with CLL/SLL, with navitoclax demonstrating a single-agent 35% overall response rate (ORR). However, navitoclax and obatoclax were limited by dose-dependent thrombocytopenia occurring days after initial dosing due to the requirement for BCL-X_L in platelet production.

To improve tolerability, the BCL-2 specific BH3-mimetic ABT-199 (venetoclax) was developed.¹⁸ Using a navitoclax-bound three-dimensional crystal structure of BCL-2, navitoclax was reverse engineered for increased specificity to the P4 hydrophobic pocket of BCL-2. This design approach

yielded a sub-nanomolar affinity to BCL-2 for venetoclax, over 200 times more specific compared to BCL-X_L. Efficacy of venetoclax in NHL cell lines correlated with BCL-2 expression levels and synergized with both bendamustine and rituximab in murine xenograft models. Importantly, venetoclax demonstrated significantly less thrombocytopenia in animal models compared to navitoclax. This prompted the investigators to test venetoclax at a dose of 100 or 200 mg in three human patients with relapsed/refractory CLL/SLL. In all three cases, reduction of palpable lymphadenopathy was detected within 24 hours and laboratory studies demonstrated evidence of tumor lysis syndrome (TLS).

These promising data led to an expanded phase I dose-escalation trial in 116 patients with relapsed/refractory CLL/SLL (M12-175), testing venetoclax doses ranging from 150 to 1,200 mg daily.¹⁹ The trial accrued a historically difficult to treat population with 89% of the patients having at least one adverse feature and a median number of three prior therapies. Venetoclax was orally bioavailable, with peak serum concentrations achieved between 6 and 8 hours, and a half-life of ~19 hours. Based on the pharmacokinetic profile, a target maximum dose of 400 mg daily was used in the expansion cohort.

The most significant adverse effect of venetoclax identified in the dose expansion cohort in the M12-175 study was TLS and was observed in patients receiving 200, 100, and 50 mg initial venetoclax dosing, resulting in one grade 5 adverse event. Another fatal TLS event occurred with the 50 mg starting dose of venetoclax in the concurrently performed M13-365 trial (discussed below). As a result, all ongoing venetoclax studies were temporarily suspended while the safety data were carefully analyzed. Consequently, several protocol amendments were made to mitigate the TLS risk. First, the starting venetoclax dose was lowered to 20 mg daily with a more gradual weekly dose escalation to the target dose of 400 mg daily over 5 weeks (20 mg → 50 mg → 100 mg → 200 mg → 400 mg). TLS prophylaxis with aggressive hydration and urate-lowering agents, such as allopurinol, were mandated and any TLS-related electrolyte abnormalities were aggressively corrected. Additionally, patients were stratified according to their risk for TLS based on the absolute lymphocyte count and presence of bulky adenopathy, with higher risk patients requiring more stringent TLS monitoring. Initially, all patients were hospitalized for TLS monitoring during the first 24 hours of each venetoclax dose escalation. After these modifications, no further clinical TLS events were observed on these studies. In the current practice guidelines, hospitalization is only required for patients with high tumor burden

and TLS risk defined as lymph node size ≥ 10 cm in diameter or lymphocyte count $>25 \times 10^9$ cells/L and lymph node size ≥ 5 cm in diameter. In addition, patients with impaired renal function may also be considered for inpatient monitoring during the initial periods of dose escalation. Patients who do not have high tumor burden or impaired renal function may have TLS monitoring done in the outpatient setting, with TLS labs monitored pre-dose, 6–8 hours, and 24 hours post-dose at each dose escalation.²⁰

The second most significant adverse event was grade 4 neutropenia observed in 28% of patients, resulting in seven episodes of febrile neutropenia. The majority of neutropenia events did not result in infectious complications and were managed with either dose reductions in venetoclax or growth factor administration. Several other grade 2 or lower adverse events were reported in over 40% of patients and included diarrhea (52%), upper respiratory tract infection (48%), nausea (47%), and fatigue (40%).

Impressively, venetoclax was active at all doses tested in this heavily pretreated population and produced a 79% ORR and 20% complete response (CR). Median time to achieve CR was 6 months, although three additional patients achieved CR after 1 year. Efficacy extended to all poor-risk subgroups analyzed, including fludarabine-resistant disease (ORR 79%) and unmutated IGHV status (ORR 76%). Even in patients harboring a *TP53* mutation or del(17p), an ORR of 71% was observed, comparable to the overall trial population. In vitro studies on primary samples from the trial further demonstrated that apoptosis induced by venetoclax occurred independently of *TP53* and the LC50 for venetoclax is similar regardless of *TP53* status.²¹ The encouraging efficacy of venetoclax prompted an expanded phase II study confirming an ORR again of 79% in 107 relapsed/refractory patients with del(17p) (M13-982).²² This led to the 2016 FDA approval for venetoclax in patients with 17p deletion with previously treated CLL/SLL.

Venetoclax and anti-CD20 immunotherapy in CLL/SLL

Antibody therapy targeting the B-cell surface antigen CD20 with rituximab is now the standard of care in a number of B-cell non-Hodgkin lymphomas. Despite low CD20 antigen expression in CLL/SLL, rituximab is still able to mediate antineoplastic properties likely through enhanced immune system clearance of malignant cells. Rituximab combined with fludarabine and cyclophosphamide chemotherapy (FCR) in fit, previously untreated patients with CLL/SLL showed a progression-free survival (PFS) and overall survival (OS)

advantage compared to patients receiving chemotherapy alone in a randomized phase III trial (the CLL8 study).²³ A second generation glycoengineered and humanized anti-CD20 monoclonal antibody, obinutuzumab, has also been FDA approved in combination with chlorambucil (G-Clb) in treatment-naïve patients unfit for standard induction immunochemotherapy after demonstrating superior PFS compared to rituximab and chlorambucil (the CLL11 trial).^{24,25}

Because of their unique mechanisms, there has been great interest in combining anti-CD20 immunotherapy with the BH3-mimetics to obtain synergistic antitumor effects. An initial phase II trial showed an ORR of 70% with the combination of rituximab and navitoclax compared to 35% with rituximab alone in untreated patients with CLL/SLL.²⁶ However, this trial terminated early due to the promising preclinical data with venetoclax.

The first study to formally validate the efficacy of venetoclax plus rituximab (VR) was the phase Ib M13-365 trial published in early 2017, which included 49 patients with relapsed or refractory CLL/SLL.²⁷ In the dose expansion cohort, patients initiated venetoclax at 20 mg which escalated weekly to a 400 mg daily dose over 5 weeks. Monthly rituximab (375 mg/m² on dose one, 500 mg/m² subsequently) was initiated 1 week after target venetoclax dose was achieved. The median number of prior therapies in the trial population was 2, with 90% of the having received prior rituximab therapy, and nearly half deemed rituximab-refractory. Despite this, VR demonstrated an 86% ORR and a 51% CR rate. As previously mentioned, this trial also had one grade 5 adverse event related to TLS occurring 1 day after an initial 50 mg venetoclax dose. After enhanced TLS prophylaxis and monitoring protocols were implemented, as well as the 5-week ramp-up starting at 20 mg, no further clinical TLS events were observed.

M13-365 prespecified bone marrow minimal residual disease (MRD) assessment as an exploratory objective. In CLL/SLL, undetectable MRD (uMRD) is defined as detecting less than one tumor cell per 10⁴ white blood cells using four-color flow cytometry. Bone marrow uMRD was achieved in 57% (28 of 49 total patients, although only 42 had samples available for analysis), a substantially higher rate than historically achieved with chemoimmunotherapy or B-cell signaling inhibitors in relapsed/refractory CLL/SLL.²⁸ The observed uMRD rate increased to 80% in patients achieving a CR. This resulted in a 2-year ongoing response in 100% for patients with uMRD compared to 71% for patients with detectable MRD.

The study protocol allowed patients the option to discontinue venetoclax after achieving a CR or bone marrow uMRD.

In total, ten patients with a CR and uMRD discontinued therapy and all remained progression free after discontinuation of therapy, including three patients remaining in remission off of venetoclax for over 12 months. Two participants with a CR with detectable MRD progressed ~24 months after venetoclax discontinuation. Importantly, both patients responded again after resuming venetoclax treatment, serving as a proof of concept that treatment discontinuation is possible upon deep response (CR and/or uMRD), and treatment reinitiation upon disease progression may be feasible with venetoclax-based therapy.

The promising efficacy of the VR combination was definitively evaluated in the phase III, international, and randomized MURANO trial comparing VR to standard immunochemotherapy.²⁹ This study randomly assigned 389 patients with relapsed and refractory CLL/SLL to receive six cycles of bendamustine plus rituximab (BR) immunochemotherapy or 2 years of continuous venetoclax therapy with 6 monthly rituximab added after the initial 5 weeks venetoclax dose escalation. The superiority of VR was impressive with a 24-month PFS of 84.9% compared to 36.3% with BR (HR 0.17), meeting the trial's primary endpoint for PFS. Secondary efficacy endpoints were also in favor of the VR combination, with a 24-month OS of 91.9% for VR compared to 86.6% with BR. The ORR, assessed at the end of combination therapy (9 months) by an independent review committee, was 92.3% for VR compared with 72.3% for BR. Additionally, the rate of CR and CR with incomplete hematologic recovery (CRi) benefited the VR combination (26.8% vs 8.2%). A preplanned subgroup analysis of patients harboring del(17p) and TP53 mutation confirmed a similar PFS benefit with VR in these groups. PB uMRD assessment was mandatory and performed at 9 months in both arms by flow cytometry and/or allele-specific oligonucleotide PCR. The VR combination achieved a PB uMRD rate of 62.4% compared to 13.3% with BR at the 9-month timepoint, and 83.5% at any time during the trial on VR. These results led to the expanded FDA approval in June 2018 for venetoclax and rituximab combination in all patients with CLL/SLL, with or without 17p deletion, who had received at least one prior therapy.

The rate of grade 3 or 4 neutropenia was slightly higher with VR (57.7% vs 38.8%), but the rate of grade 3 or 4 febrile neutropenia and infections were lower than with BR (3.6% vs 8.5%), with comparable use of growth factor between both groups. Using the venetoclax dose escalation and TLS prophylaxis protocols developed in the M13-365 trial, the frequency of clinical TLS was reduced to 3.1%, and there

were no grade 5 events. Overall, adverse events leading to discontinuation of treatment were nearly identical in both groups, ~9%. However, a larger number of dose interruptions and reductions were observed in patients receiving VR, driven by a higher frequency of neutropenia. When interpreting this, however, it is important to recognize the longer therapy duration of VR compared to BR (2 years vs 6 months) and that the number of total infections on VR was lower than BR (17.5% vs 21.8%). As with all novel therapies, ongoing monitoring of patients on the MURANO trial, as well as other venetoclax-based studies, will be essential for identifying any additional or delayed toxicities.

In regards to the primary PFS endpoint in the MURANO trial, the observed PFS benefit could be somewhat inflated by the number of del(17p) and TP53-mutated patients receiving BR (23.6% and 26.2%, respectively), a population known to have poor responses to immunochemotherapy. In clinical practice, relapsed/refractory patients with del(17p) would have likely received an alternative B-cell signaling inhibitor rather than BR. Admittedly though, this should not take away from the clinical benefit observed virtually in all subgroups analyzed in the MURANO trial.

As data from the MURANO and M13-365 trials mature, a key area of interest is the high uMRD rates obtained with VR, as this is rarely observed with B-cell signaling inhibitors.³⁰ It appears that uMRD correlates with and, thus, may be a feasible surrogate marker for duration of response. There are a few considerations to be aware of when interpreting the uMRD data from the MURANO study and comparing them to other trials. First, unlike the bone marrow-based MRD assessment in M13-365 study, MRD assessments in the MURANO trial were mostly performed from PB samples (94.1%), with only 29.6% of patients had MRD tested in the bone marrow.³¹ In MURANO, the patients with paired PB and bone marrow aspirate samples had 84% concordance in results, suggesting that PB analysis may be sufficient for a disease response assessment for this regimen, although this should not be generalized for other treatments. Second, MURANO assessed MRD by both flow cytometry and a more sensitive allele specific oligonucleotide PCR using patient specific primers. Detectable MRD was defined by either test being positive, which may increase the sensitivity of the detection. The percentage of patient's achieving uMRD was similar in the MURANO and M13-365 trials, which gives additional confidence in the uMRD results of both trials. Finally, the MURANO protocol specified MRD assessment after combination therapy, 9 months after initiation of venetoclax. It is possible this timepoint underestimated the

total uMRD rate as approximately a quarter of the patients in M13-365 achieved uMRD after 9 months while on venetoclax monotherapy.

With a maturing 3-year median follow up, all patients have completed venetoclax maintenance on the MURANO trial.³² The rate of progression in the first 12 months after completion of therapy was 13% and almost all of these patients (14 of 16) were MRD-intermediate or high positive in the PB at the time of venetoclax discontinuation reemphasizing the importance of uMRD guiding therapy discontinuation. Sixty-nine percent of patients with uMRD at time of therapy discontinuation remained in uMRD, with the majority of conversions occurring to intermediate-MRD and not true clinical progression.³³ Patients with clinical progression or conversion to detectable MRD after venetoclax discontinuation were enriched for *TP53* mutations and del(17p). No new safety signals were identified after 2 years of venetoclax maintenance and efficacy data for median PFS (NR vs 17.0 months) and 3-year OS (87.9% vs 79.5%) strongly favor VR.

Predictive modeling does suggest that there is unlikely to be further improvement of response to additional venetoclax beyond 2 years of total therapy as pooled analysis of all VR trials demonstrated a bone marrow uMRD rate plateauing at 63% at 24 months of total venetoclax therapy.³⁴ These same models also predict many patients with uMRD will continue to hold durable remissions off of therapy. Regardless of the durability of the uMRD, the MURANO trial confirms the synergy of venetoclax with rituximab in CLL/SLL and supports further clinical investigation of venetoclax in the frontline setting and with other molecular therapies.

Novel combinations with venetoclax in CLL/SLL

Fortunately, for most patients, CLL/SLL is a disease managed over many years and even decades. Because of this, it is important to consider both the short and long-term toxicities of treatments giving the increasing lifespan of CLL/SLL patients. While chemoimmunotherapy regimens can produce durable remissions (ie, FCR or BR), they are associated with treatment-related myelodysplasia and leukemia (tMDS/AML) that can manifest years after chemotherapy exposure.³⁵ Median patient follow-up of CLL8 study was 5.9 years at last update, and at that time the rate of tMDS/AML was between 2% and 3%.

In addition to obinutuzumab, the past decade has seen the development and approval of several molecular inhibitors of B-cell receptor (BCR) signaling in CLL/SLL: ibrutinib (BTK inhibitor), idelalisib (PI3K δ inhibitor), and duvelisib (PI3K δ

and PI3K γ inhibitor).^{25,36–38} Acalabrutinib, a BTK inhibitor with approval in Mantle cell lymphoma, also has activity in CLL/SLL but is not currently FDA approved.³⁹ While BCR signaling inhibitors have high ORRs in CLL/SLL (79% ORR for ibrutinib in a relapsed/refractory setting),²⁸ these agents rarely achieve uMRD and is recommended to continue until progression.⁴⁰ Given their distinct cellular targets, it is hypothesized that these agents may be combined with other approved agents for synergy without substantially increased toxicity. Supporting this, preclinical data have demonstrated that ibrutinib therapy increases dependence of CLL/SLL cells on BCL2, leading to added sensitivity to venetoclax.⁴¹ A similar synergism has been observed when venetoclax is combined with PI3K inhibition.⁴² Thus, various combinations of anti-CD20 immunotherapy, B-cell signaling inhibitors, and venetoclax are being tested with the hope of minimizing exposure to cytotoxic chemotherapy given early in the disease course.

The safety of venetoclax plus ibrutinib (VI) combination was first evaluated in relapsed/refractory disease and as initial therapy in high-risk CLL/SLL.⁴³ Patients were assigned to receive a 3-month ibrutinib monotherapy lead followed by VI combination therapy. Combination therapy continued for total of 2 years with the option for ibrutinib discontinuation in patients achieving bone marrow uMRD. Patients with detectable MRD could continue ibrutinib monotherapy. At last update, CR/CRi rate was 92% with 68% of patients achieving bone marrow uMRD at 12 months, substantially higher than with either agent alone.⁴⁴ The larger CLARITY trial is also investigating the VI combination in patients with relapsed disease. At the latest update, after 12 months of combined therapy 58% of patients achieved CR/CRi and the same percentage of patients achieved uMRD in the PB.⁴⁵

While an entirely oral therapy regimen, such as VI, is appealing to many patients, incorporating an anti-CD20 immunotherapy backbone is likely to boost efficacy based on the high uMRD rates in MURANO trial. Given the superior PFS of obinutuzumab to rituximab in combination with chlorambucil in the CLL11 trial, the majority of the combination regimens under study include obinutuzumab (Table 1). A phase IB/II trial in the relapsed/refractory setting has confirmed the tolerability of obinutuzumab with ibrutinib and venetoclax (GVI) with promising early reports of efficacy and tolerability.^{46,47}

Venetoclax-based regimens as initial treatment in CLL/SLL

The next critical issue under study is verifying and comparing venetoclax combinations with standard of care

Table 1 Selected clinical trials testing venetoclax-based regimens in CLL/SLL

Clinical trial ID	Name	Design	Eligibility	Treatment arm(s)
NCT02950051	CLL13 (GAIA)	Phase III, randomized	Fit patients, treatment naïve, TP53/del(17p) excluded	1. FCR or BR 2. VR 3. GV 4. GVI
NCT02242942	CLL14	Phase III, randomized	Unfit patients, treatment naïve, TP53/del(17p) included	1. G-Cbl 2. GV
ISRCTN01844152	FLAIR	Phase III, randomized	Fit patients, treatment naïve, TP53/del(17p) excluded	1. FCR 2. Ibrutinib 3. IR 4. VI
NCT03462719	–	Phase III, randomized	Unfit patients, treatment naïve, TP53/del(17p) excluded	1. G-Cbl 2. VI
NCT02910583	CAPTIVATE-2	Phase II, randomized	Fit patients, treatment naïve, TP53/del(17p) included	1. Ibrutinib 2. VI
ISRCTN13751862	CLARITY	Phase II, single-arm	Prior purine analog therapy, TP53/del(17p) included	1. VI
NCT03379051	–	Phase I/II, single-arm	One prior treatment regimen, TP53/del(17p) included	1. Venetoclax in combination with ibrutinib and umbralisib
NCT03534323	–	Phase I/II, single-arm	One prior treatment regimen, TP53/del(17p) included	1. Venetoclax plus duvelisib
NCT02639910	COSMOS	Phase II, single-arm	Prior BTKi therapy, TP53/del(17p) included	1. Venetoclax or idelalisib + MOR208
NCT02427451	–	Phase I/II, single-arm	One prior treatment regimen, TP53/del(17p) included	1. GVI

Notes: Venetoclax-based clinical trials under investigation in CLL/SLL. Further details on specific agents: ibrutinib is a novel anti-CD20 antibody, umbralisib is a novel PI3K δ inhibitor, and MOR208 is a novel anti-CD19 antibody.

Abbreviations: BR, bendamustine, rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; FCR, fludarabine, cyclophosphamide, rituximab; G-Cbl, obinutuzumab, chlorambucil; GV, obinutuzumab, venetoclax; GVI, obinutuzumab, venetoclax, ibrutinib; IR, ibrutinib, rituximab; VI, venetoclax, ibrutinib; VR, venetoclax, rituximab.

immunochemotherapy in previously untreated patients. This past year, the first efficacy data of VI in frontline session was presented from the CAPTIVATE-2 trial.⁴⁸ In this phase II trial, a similar protocol to CLARITY was used with 3 months ibrutinib lead-in to minimize TLS prior to combination VI. Early data are promising with an uMRD rate of 82%, achieved with a favorable safety profile. While higher than MURANO and M13-365, one would expect a more favorable response in the treatment-naïve population compared to relapsed/refractory patients. CAPTIVATE-2 also plans to address the critical question of length of therapy by randomizing patients that are uMRD after 12 cycles of VI to receive ibrutinib monotherapy maintenance or placebo.

While the results from CAPTIVATE-2 are encouraging, two ongoing randomized trials in the frontline setting, CLL13, a study organized by the German CLL/SLL study group, and FLAIR, run through the UK, will hopefully define the new standard of care in frontline CLL/SLL management who are candidates for chemoimmunotherapy.⁴⁹ The co-primary endpoints of both trials are PFS as well as rate of

uMRD (PB flow cytometry in CLL13 and bone marrow flow cytometry in FLAIR). CLL13, which is focused on defining the optimal venetoclax-based regimen, assigns treatment naïve patients in 1:1:1:1 ratio to receive six cycles of standard of care chemotherapy (FCR or BR) or three experimental arms: VR, GV, or GVI.⁵⁰ Venetoclax will be administered in combination with anti-CD20 therapy for six cycles and continued for six additional cycles, while ibrutinib is continued until uMRD is achieved or for a maximum of 3 years. The FLAIR trial is randomizing untreated patients with CLL/SLL in 1:1:1:1 ratio to FCR immunochemotherapy or three versions of ibrutinib therapy: ibrutinib monotherapy, IR, or VI.⁵¹ Ibrutinib and venetoclax therapy can be continued for up to 6 years or discontinued if uMRD is attained. Both of these trials will be the first opportunity to compare VI and other venetoclax-based or ibrutinib-based novel chemotherapy free regimens to our standard chemotherapy strategies in the frontline setting.

For unfit patients with medical comorbidities and thus not candidates for intensive immunochemotherapy, a randomized

prospective phase III trial comparing G-Cbl with GV is likely to define the superior frontline treatment regimen (CLL14, Table 1). Similar to CLL13, venetoclax will be administered for six cycles with obinutuzumab and continued for six cycles as monotherapy. While the single primary outcome measure is PFS, MRD will be assessed by PCR and reported as a secondary outcome. Initial run-in data have been reported for CLL14 and 11 of 12 patients analyzed achieved uMRD in the PB at 3 months after the completion of combination therapy.⁵² The trial sponsor has also recently announced that the trial has met its primary endpoint, with presentation of the data expected soon.⁵³

Even if the FLAIR and CLL13 trials confirm the superiority of a non-chemotherapy option in the frontline setting, there will likely still be clinical scenarios where chemotherapy can be considered. As mentioned above, follow-up on the CLL8 trial, which initially confirmed the efficacy of FCR, continues to mature, and there appears to be highly durable remissions and possible cures in up to half of the patients with hypermutated IgVH.³⁵ Other investigators are proposing an induction and maintenance approach, using chemotherapy for initial debulking followed by a maintenance phase with anti-CD20 therapy and venetoclax.⁵⁴ This strategy could be tailored to patients at high risk for TLS, but whether initial anti-CD20 or ibrutinib induction alone achieves the same goal could be argued. Finally, due to different reimbursement categories and copays, a defined treatment period with chemotherapy is less financially toxic than prolonged with maintenance therapy with the novel oral agents whose annual retail cost is over \$100,000. The current clinical trials defining a treatment duration and possible discontinuation of therapy based on uMRD status will also hopefully lower the financial burden of CLL/SLL management.

Conclusion

The oral BCL2 inhibitor venetoclax has been shown to be highly effective in CLL/SLL. Venetoclax combinations with anti-CD20 monoclonal antibody or BCR pathway inhibitors demonstrated the potential to produce high quality response, including high rates of uMRD, which allows treatment discontinuation with sustained duration of response. Therefore, venetoclax-based therapy provides a feasible option for fixed-duration therapy, thus distinguishing venetoclax from the BCR pathway inhibitors which requires continuous treatment. Multiple ongoing large randomized clinical trials comparing venetoclax-based therapy with conventional immunochemotherapy or ibrutinib-based therapy will help to determine the optimal frontline treatment options. There is

still much to learn about the optimal duration of venetoclax treatment and maturation of our current clinical trial data will address the durability of remissions once maintenance therapy is discontinued. Re-treatment with venetoclax after disease relapse off therapy is another area of interest. With multiple oral targeted therapies available for CLL/SLL, there is limited experience with subsequent treatment after failing one oral agent and the optimal sequence of treatment remains to be determined.^{55,56} This is likely to become clearer as we become more experienced with these therapies. Regardless of these uncertainties, the progress already made has resulted in practice changing therapies that have improved outcomes in CLL/SLL patients.

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