Chronic Lymphocytic Leukemia

Abstract 797

Utilization and Early Discontinuation of First-Line Ibrutinib for Patients with Chronic Lymphocytic Leukemia Treated in the Community Oncology Setting in the United States

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Introduction: Ibrutinib, an orally and continuously administered Bruton tyrosine kinase inhibitor, allows for targeted, non-chemotherapy based treatment for chronic lymphocytic leukemia (CLL). While the initial US marketing approval for ibrutinib in CLL was for relapsed disease (February 2014), several trials have since shown favorable efficacy in the first-line setting. Ibrutinib was well tolerated in these pivotal studies, with discontinuation occurring in less than 9% at 12 months (O'Brien et al., *Am J Hematol.* 2019). Most early ibrutinib discontinuations in the first-line setting are due to adverse events (Tedeschi et al., EHA 2019), and optimal strategies to manage ibrutinib-related toxicities are not well defined. We hypothesized that ibrutinib is increasingly utilized for first-line treatment of CLL during routine management in the US, but that ibrutinib discontinuation rates for the real-world population are greater than those reported in clinical trials. Further, we expected to find greater odds of discontinuation in older adults and those with poor performance status, two groups underrepresented in clinical trials.

Methods: We conducted a retrospective cohort study of CLL patients treated at community oncology practices using the nationwide Flatiron Health database. The Flatiron Health database is a longitudinal, demographically and geographically diverse database derived from de-identified electronic health record data from over 280 cancer clinics in the US. All patients initiated CLL therapy in the first-line setting between March 1, 2014 and February 28, 2019. We first assessed trends in the use of first-line ibrutinib (i.e., ibrutinib with/without an anti-CD20 antibody). We then focused on patients who received ibrutinib and had at least 180 days of available follow up or had died within this period. We used multivariable logistic regression to assess the association of patient characteristics with early discontinuation (defined as stopping within 180 days of initiation). Covariates included in our model were patient age, sex, race, insurance type, ECOG performance status, year of treatment, time from CLL diagnosis to ibrutinib initiation, chromosome 17p status, and geographical region.

Results: We identified 5,634 individuals initiating first-line treatment for CLL, of whom 1,639 (29.1%) received an ibrutinib-based regimen. Use of ibrutinib in the first-line setting increased over time (Cochrane-Armitage test for trend, p <.001; Figure 1), making up approximately 40% of first-line CLL initiations by late 2018. Of the

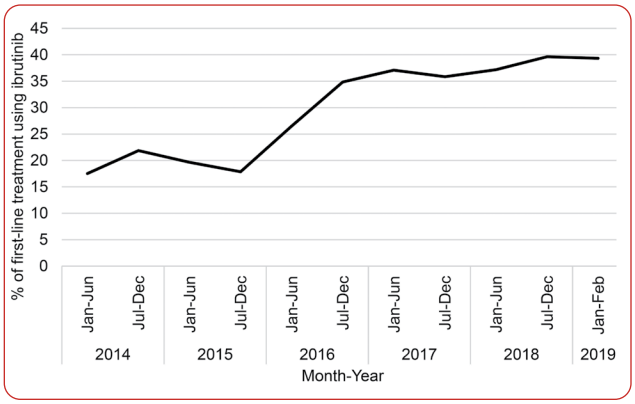

Figure 1. Proportion of first-line treatment initiations for chronic lymphocytic leukemia using ibrutinib in the United States community oncology setting.

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1,497 individuals with adequate follow up, early discontinuation of ibrutinib occurred in 16.2%. Early discontinuation of ibrutinib was more common in individuals aged ≥80 years (26.2% vs. 9.4% for individuals 60-70 years old), those requiring treatment within 1 year of their CLL diagnosis (22.1% vs. 14.8% for those with CLL diagnosis ≥5 years prior to ibrutinib initiation), and those with ECOG performance status of 2 or greater (33.8% vs. 10.2% for ECOG = 0). On multivariable logistic regression, older age (≥80 years vs. 60-70 years, adjusted odds ratio (aOR) = 2.94, 95% confidence interval (CI) 1.79–4.76, p <.001) and worse performance status (ECOG ≥2 vs 0, aOR = 3.45, 95% CI 2.16–5.53, p <.001) remained independently associated with increased odds of early ibrutinib discontinuation.

Conclusion: While ibrutinib was increasingly utilized in the first-line setting for CLL within our large representative US community patient cohort, early discontinuation was more common than reported in pivotal trials. Given the complexity of the rapidly changing CLL treatment landscape, clinical decision support tools and other modern cancer care delivery approaches should be explored to improve administration of novel CLL therapies in the real-world setting.

The Advanced Practitioner Perspective: Sandra E. Kurtin, PhD, ANP-C, AOCN®

Ibrutinib was approved in 2014 for the treatment of relapsed/refractory chronic lymphocytic leukemia (CLL). Since that time, there have been a number of approvals across many lymphoid malignancies. Early discontinuation across those trials, including the frontline use of ibrutinib in CLL, has been roughly 9% at 12 months of treatment.

This is an important retrospective cohort study by Flatiron Health evaluating 280 community practices that was conducted between March 2014 and February 2019. There were 5,634 patients receiving frontline therapy for CLL in this analysis. 29% of those patients, or 1,639, received an ibrutinib-containing regimen. Importantly, in the final year of the study, in 2018, the number of patients receiving ibrutinib-containing regimens increased to 40%.

Included in this analysis was the evaluation of covariates: age, sex, race, Eastern Cooperative Oncology Group (ECOG) status, the presence or absence of 17p, how long had the patient been diagnosed between the time of diagnosis to treatment, and also what region of the country they lived in. The outcomes show that age greater than 80, ECOG status of 2 or greater, or having been diagnosed within a year of starting treatment, implying that these patients probably had CLL for some time, were all associated or correlated with early discontinuation of therapy. Most often, discontinuation was due to adverse events. The most common adverse events across trials with ibrutinib were infections, including pneumonia, and cytopenias.

Trial Design

I think it is important for us as advanced practitioners to understand how studies are run, who was included in the original trials, and how we are applying that to the patients in real life in our practice.

Most clinical trials have fairly standard inclusion and exclusion criteria based on organ function for drug metabolism (renal, hepatic) and tolerance (heart, lung). Familiarity with these criteria is essential to deciding whether the agents can be used in the way they are administered in the trial. Guidelines for dose modifications for organ impairment and for treatment-related adverse reactions are included in all package inserts at the time of drug approval based on the experiences gleaned from the clinical trial.

Familiarity with this information will allow the advanced practitioner to individualize treatment for each patient if needed. Importantly, this study was focused on patients in community settings, which is generally more representative of the general population than patients at tertiary centers or enrolled in clinical trials.

Geriatric Assessment

Applying geriatric assessment tools prior to starting treatment in patients with hematologic malignancies can improve the tailoring process and improve treatment tolerance (Klepin, 2019). Drug discontinuation is more common in patients who are unfit compared

to those who are fit, and the risk of grade ≥ 3 adverse events is higher in this group. Assessing fitness prior to starting treatment has become more common; however, this is a dynamic process that requires reassessment through the course of treatment. This serial or longitudinal approach to fitness can guide treatment modification to improve tolerance by reducing the severity and duration of adverse events (Lin & Klepin, 2019).

Maximizing each treatment option by applying strategies for tolerance and reducing the probability of more severe adverse events is critical to achieving the best possible outcome. Across a broad range of attributes, age ≥ 80, a poor performance status (ECOG ≥ 2), being recently diagnosed with CLL, and met criteria for treatment were the factors associated with early discontinuation of therapy. Knowing this, the advanced practitioner may employ a number of strategies to improve tolerance in this group, including collaboration with other health-care providers to improve management of comorbidities, more frequent visits to monitor and manage toxicities, and use of dose modification strategies earlier in the process of treatment to mitigate the severity of adverse events.

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Abstract 502

Efficacy of Therapies Following Venetoclax Discontinuation in CLL: Focus on B-Cell Receptor Signal Transduction Inhibitors and Cellular Therapies

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Introduction: Venetoclax (VEN) based therapy has become a standard of care in front line and relapsed-refractory (R/R) CLL based on favorable efficacy and toxicity. Whereas prospective data regarding activity of therapies following ibrutinib (IBR) or idelalisib (IDE) are available in the settings of progression (VEN, non-covalent BTKi) and intolerance (acalabrutinib), how best to manage patients (pts) who discontinue (dc) VEN remains a key unanswered question. With the increased use of VEN in early lines of therapy (LOT; CLL 14, MURANO), the activity of BTK inhibitors (BTKi) and cellular therapies following VEN becomes a critical issue. No prospective study has addressed this question, and currently reported VEN clinical trials have limited information about subsequent treatments. While recent data describe VEN resistance mechanisms (Guieze 2018, Blombery 2019), the impact of VEN resistance on efficacy of post VEN therapies is unknown. To address this gap, we conducted an international study to identify a large cohort of pts who dc VEN and have been subsequently treated.

Methods: We conducted an IRB approved multicenter (31 US, EU, South American sites, in partnership with UK CLL Forum and CORE registry), retrospective cohort study of CLL pts who dc VEN for any reason. We examined demographics, dc reasons, responses, survival, adverse events (AEs) and activity of post VEN therapies. Primary endpoints were overall response rate (ORR) and progression free survival (PFS) for the post VEN treatments stratified by treatment type (BTKi, PI3Ki and cellular therapy: CAR-T or alloHSCT). ORR was defined by iwCLL criteria and PFS was defined from VEN dc to disease progression (PD), death, or last follow up for next treatment. Pts were further stratified by BTKi (resistant/intolerant) and PI3Ki exposure prior to VEN. PFS-2 was defined as time from VEN start to tumor progression on IBR or death from any cause.

Results: 326 CLL pts who dc VEN in the front line (4%) and R/R settings (96%) were identified. The cohort was 69% male, 87% white, median (med) age 66 (38-91) at VEN start, 27% treated with VEN based combinations (n=88, med 6 cycles anti-CD20 abs). Pre VEN prognostic features: 82% IGHV unmutated (n tested=166), 47% del17p (n=306), 45% TP53 mut (n=217), 39% complex karyotype (n=273), 23% BTK mut (n=79), 18% NOTCH1 mut (n=103), 10% PLCγ2 mut (n=74).

Pts received med 3 therapies (0-11) prior to VEN; 40% were BTKi naïve (n=130), 60% were BTKi exposed (196) and 81% were IDE naïve (n=263). Most common reasons for VEN dc were PD (38%), AE (20%), Richter's transformation (RT, 14%), 8% pt preference, and HSCT 5%.

Of 326 pts who dc VEN, 188 (58%) were treated with a subsequent LOT, 61 are alive and untreated and 77 died prior to a subsequent LOT. Post VEN sequencing analyses focused on BTKi, PI3Ki and cellular therapy (CAR-T or alloHSCT) activities following VEN dc (Table1). ORR to BTKi was 84% (n=44) vs. 54% (n=30, p<.001 for ORR) in BTKi naïve vs. exposed patients (estimated med PFS 32 months (M) for BTKi naïve, 4 M in BTKi resistant, not reached in BTKi intolerant; Figure 1AB). ORR to PI3Ki was 47% in PI3Ki naïve pts following VEN, though responses were not durable (med PFS 5 M; Figure 1C). 66% responded to CAR-T post VEN (n=18), med PFS 9 M; med PFS was not reached for 19 pts who underwent alloHSCT post VEN (Fig-

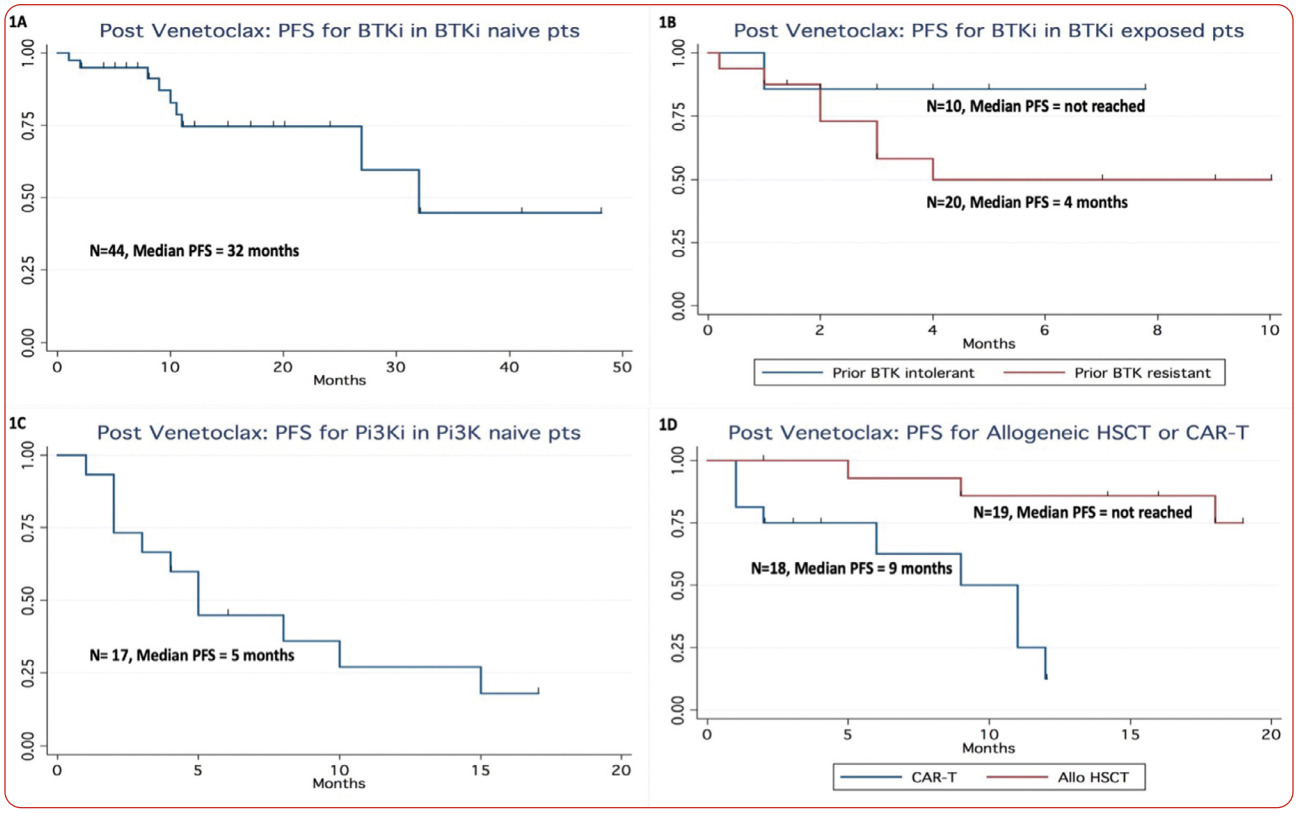

Figure 1. PFS for patients previously treated with venetoclax. (A) BTK inhibitor–naive patients subsequently treated with BTK inhibitors. (B) BTK inhibitor–exposed patients subsequently treated with BTK inhibitors divided by reason for prior discontinuation of BTK inhibitor (intolerance vs. resistance). (C) PI3K inhibitor–naive patients subsequently treated with PI3K inhibitors. (D) Patients treated with cellular therapies including CAR-T and allogeneic hematopoietic stem cell transplant.

ure 1D). Med PFS-2 for pts treated with VEN followed by IBR was not reached with med follow up 22 M (24 M PFS 78%, Figure 2). Med PFS for RT pts treated post VEN was 5 M (variable therapies).

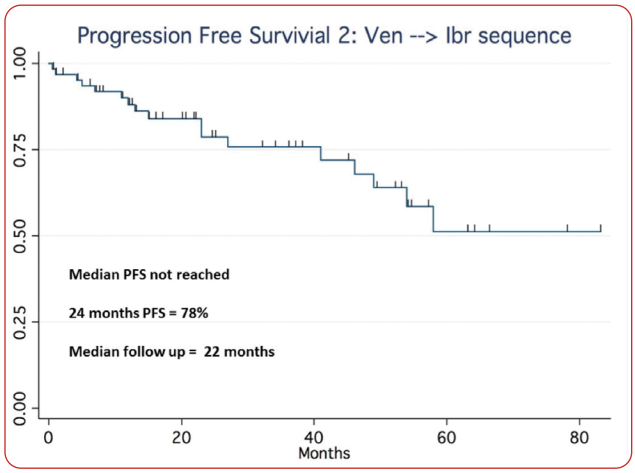

Figure 2. Time to second objective disease progression (PFS2) for patients treated with venetoclax followed by ibrutinib in the R/R setting.

Conclusions: In the largest experience of therapies following VEN dc in CLL, we demonstrated that therapy selection following VEN requires consideration of prior novel agent exposure and reasons for discontinuation. For BTKi naïve pts, selection of a covalently binding BTKi results in high ORR and durable remissions. PFS-2 data provide reassurance for using VEN prior to IBR. For BTKi exposed pts, BTK inhibition is not effective in the setting of BTKi resistance but should be considered if prior BTKi intolerance. PI3K inhibition following VEN does not appear to result in durable remissions even in PI3Ki naïve pts, suggesting possible overlap in resistance mechanisms (BTK or VEN with PI3K). We conclude that BTKi in naïve or previously responsive pts and alloHSCT following VEN appear to be the most effective strategies with durable responses. These data suggest that a number of effective regimens exist for post VEN pts, providing support for VEN use earlier in the course of CLL.

The Advanced Practitioner Perspective: Sara Tinsley, PhD, APRN, AOCN®

This is an exciting time in the treatment of patients diagnosed with chronic lymphocytic leukemia (CLL). We have moved away from treatment with intravenous chemotherapy regimens into an era of effective oral therapies. The FDA has approved several oral treatments for CLL focused on the B-cell signal transduction pathway in the past 5 years. These therapies are improving survival, especially for patients with CLL who have unfavorable prognostic features (e.g., 17p deletion, p53 mutation, complex karyotype, unmutated immunoglobulin heavy-chain variable).

This abstract presented data for how to manage patients following discontinuation of venetoclax based on a retrospective cohort study of patients who discontinued venetoclax and were subsequently treated. This was an institutional review board–approved, international, multicenter study involving 326 patients who discontinued venetoclax. Similar to other studies, this was a predominantly white (87%) and male (69%) cohort. Venetoclax discontinuations were due primarily to progressive disease (38%), adverse events (20%), and Richter's transformation (14%).

Primary endpoints for the study were overall response rate (ORR) and progression-free survival (PFS). Post-venetoclax treatments were divided into three groups, including Bruton tyrosine kinase inhibitor (BTKi), phosphoinositide 3-kinase inhibitor (PI3Ki), and cellular therapy. The ORR to BTKi was 84% (n = 44) in BTKi-naive patients compared with 54% (n = 30) in BTKi-exposed patients. The median PFS for BTKi-intolerant patients has not been reached, which is exciting. As may be expected, the PFS for BTKi-resistant patients was short at 4 months. Results for ORR to idelalisib was 47%; however, the median duration of response was short at 5 months. In cellular therapy, chimeric antigen receptor T-cell therapy patients had a good response rate at 66%; however, PFS was short at 9 months. Nineteen patients underwent allogeneic hematopoietic stem cell transplant with median PFS not reached.

Implications for the Advanced Practitioner

For advanced practitioners, this is a data-dense study with gold nuggets that can provide guidance for the sequence of CLL treatment following venetoclax discontinuation. This retrospective study provides evidence that there are effective treatments for CLL patients who have already been treated with venetoclax. The most effective therapies include allogeneic hematopoietic stem cell transplant and ibrutinib for patients who are venetoclax intolerant or BTKi naive. In providing care to CLL patients, advanced practitioners can assist patients in understanding the prognostic features of their disease and the indications for treatment.

This study represents CLL patients with adverse prognostic features, and applies primarily to the care of this subset of CLL patients. Advanced practitioners are on the front line and can advocate for clinical trial participation for future venetoclax discontinuations to provide a higher level of evidence for the treatment of patients with CLL.

Abstract 1751

A Randomized Phase III Study of Ibrutinib Plus Obinutuzumab Versus Ibrutinib Plus Venetoclax and Obinutuzumab in Untreated Older Patients (≥ 70 Years of Age) With Chronic Lymphocytic Leukemia (CLL)

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Background: The phase 3 trial A041202 solidified the Bruton's Tyrosine Kinase (BTK) inhibitor ibrutinib as a standard of care for older patients with previously untreated CLL by showing superior progression-free survival (PFS) as compared with bendamustine plus rituximab. While ibrutinib is highly effective in previously untreated CLL, there do remain disadvantages to this therapy, specifically the low rate of complete response (CR) and therefore the need for continuous administration, which increases cost and toxicity. In older patients especially, toxicities with ibrutinib are common; 17% of patients had atrial fibrillation and 29% had grade 3 or higher hypertension on the A041202 study. Thus, strategies to decrease the exposure time to ibrutinib are of interest. Venetoclax is an inhibitor of BCL2 that has shown efficacy as a single agent and in combination with monoclonal antibodies, specifically the anti-CD20 monoclonal antibody obinutuzumab for patients with previously untreated CLL. One significant advantage to venetoclax is the ability to produce CRs and minimal residual disease negative (MRD–) responses. In this study, we compare ibrutinib plus obinutuzumab (IO) to ibrutinib plus venetoclax plus obinutuzumab (IVO) with a response-dependent discontinuation. While other studies have been designed with the goal of discontinuation of ibrutinib through combinations with venetoclax, no other study has been presented using a response-dependent discontinuation strategy.

Study Design and Methods: A041702 is a randomized phase 3 study led by the Alliance for Clinical Trials in Oncology that is currently enrolling through the NCI National Clinical Trials Network (NCTN).

CLL patients age 70 years or older who are previously untreated and in need of therapy are eligible. Previous treatment of autoimmune complications with steroids or rituximab is allowed. Patients must have intermediate- or high-risk Rai stage, ECOG performance status 0-2, ANC ≥ 1000/mm^3 unless due to marrow involvement, and platelets ≥ 30,000/mm^3. CrCl must be ≥ 40 mL/min and AST/ALT ≤ 2.5x upper limit of normal. Patients with hepatitis B must have undetectable viral load, and patients must not have an intercurrent illness that is expected to limit survival to < 5 years. Warfarin and strong inhibitors or inducers of CYP3A4/5 are not permitted.

Patients are initially preregistered to the study and submit a peripheral blood sample for central FISH analysis of del(17p). Patients who are registered are randomized 1:1 to Arm 1 (IO) or Arm 2 (IVO), and are stratified by Rai stage and presence of del(17p). IO consists of I daily starting cycle 1 day 1, and O dosed as standard starting cycle 1 day 1 and continuing to cycle 6 day 1. IVO consists of IO as in Arm 1, with V starting cycle 3 day 1 with standard 5-week ramp-up and continuing until cycle 14 day 28. At the end of 14 cycles, patients in both arms undergo response evaluation with central peripheral blood and bone marrow MRD testing. Patients on IO then continue I indefinitely. Patients on IVO who are in a bone marrow MRD-CR discontinue all therapy, and those who are not continue I indefinitely.

The primary objective of the study is to compare PFS between IO and IVO using the strategy of response-dependent discontinuation. There is 90% power to detect a hazard ratio for PFS of 0.55 (corresponding to 5-year PFS rates of 70% and 82.187% for IO and IVO, respectively), at a one-sided significance level of 0.025 by a log-rank test. This design requires 128 events and 431 total evaluable patients assuming uniform accrual over the course of 3 years and minimum follow-up of 5 years. The study includes two interim analyses for superiority when 50% and 75% of the expected number of events have been observed and three interim analyses for futility when 25%, 50%, and 75% of the expected number of events have been observed.

Conclusions: A041702 is an ongoing phase 3 clinical trial using a novel response-dependent discontinuation method. Results of this study have the potential to change the standard of care for older patients with previously untreated CLL. The study is expected to accrue for 3 years beginning January 2019, and we welcome participation from sites throughout the NCTN.

The Advanced Practitioner Perspective: Amy Pierre, ANP-BC

Previously published studies have demonstrated ibrutinib, the oral Bruton tyrosine kinase inhibitor, as a standard-of-care therapy for the treatment of chronic lymphocytic leukemia (CLL). Ibrutinib has been known to achieve high response rates and lengthen progression-free survival; however, it can also carry a challenging side-effect profile for older patients, including risks for bleeding, cytopenias, cardiac arrhythmias, infections, and hypertension. Additionally, achieving a complete response is rare on this therapy; therefore, patients must continuously remain on ibrutinib to control their CLL until toxicity or progressive disease.

The Alliance trial, a phase III study that will start accruing over 3 years beginning in early 2020, is looking at the use of ibrutinib in combination with venetoclax (a BCL-2 inhibitor) and obinutuzumab (an anti-CD20 monoclonal antibody) vs. ibrutinib and obinutuzumab alone in untreated, older CLL patients, specifically patients over the age of 70. The primary endpoint of this study will be progression-free survival.

To participate in this trial, patients must demonstrate adequate blood counts and have intermediate- to high-risk Rai staging. Patients will be stratified by their Rai stage and the presence of del 17p (a known poor prognostic indicator in CLL) by fluorescence in situ hybridization testing. What is interesting about this trial is that this novel triplet therapy will be administered in a response-dependent discontinuation strategy; this entails evaluating for minimal residual disease (MRD) at the conclusion of 14 cycles of either arm of therapy. For patients in the triplet arm (ibrutinib, venetoclax, obinutuzumab) who are MRD negative at the end of 14 cycles, they will discontinue all therapy. If patients in the triplet arm are MRD positive, they will continue ibrutinib. For patients in the doublet arm of ibrutinib/obinutuzumab, they continue ibrutinib indefinitely after 14 cycles irrespective of MRD status.

The results of this phase III trial will be exciting to see, as we have already established promising data from the earlier phase II study that demonstrated 67% of previously untreated CLL patients receiving the triplet arm of ibrutinib, venetoclax, and obinutuzumab achieved MRD negativity.

Implications for the Advanced Practitioner

As advanced practitioners, we are always looking for a more individualized approach to caring for our patients, as well as strategies to reduce toxicity and improve quality of life. This study could demonstrate a more elegant approach to treating our older CLL patients, as it is a tailored therapy based on response criteria. In addition, this trial has the potential to change the standard of care for our older untreated CLL patients with a chemotherapy-free therapy, and possibly a pill-free strategy if they achieve MRD negativity. There are many older patients who are unable to safely receive chemotherapy or have the ever-growing problem of polypharmacy, and this trial may demonstrate an efficacious solution to these pertinent issues.

All three agents in the triplet arm can cause hematologic toxicity, and the most frequent cytopenias were thrombocytopenia and neutropenia in the earlier phase II trial. Anticipating hematologic toxicity from this triplet combination is a key role as an advanced practitioner, as well as providing instructions on infection and bleeding precautions.

It will be exciting to see the results of the phase III Alliance trial, since patients will be treated for a fixed duration based on MRD testing and have the opportunity to be potentially therapy free after only a little over 1 year of definitive therapy if they truly achieve MRD negativity.