5 Minute JournalClub

POST-ASH Issue 4, 2014

BCL-2 Inhibitor ABT-199 Monotherapy for High-Risk Relapsed/Refractory CLL or SLL

For more visit ResearchToPractice.com/5MJCASH2014

Research To Practice®

CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on the management of chronic lymphocytic leukemia (CLL) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Apply recent clinical research findings with the newly FDA-approved combination of obinutuzumab and chlorambucil to the management and care of patients with previously untreated CLL.
- Develop an understanding of emerging efficacy and side-effect data with novel agents and combination regimens — including next-generation anti-CD20 antibodies and PI3 kinase, Btk and BCL-2 inhibitors — under evaluation for previously untreated and relapsed/refractory CLL and, where appropriate, facilitate patient access to ongoing trials of these agents.
- Evaluate recent clinical findings with the newly FDA-approved Btk inhibitor ibrutinib, alone and in combination with chemotherapy, for patients with CLL with and without deletion 17p or those with relapsed/refractory disease.
- Compare and contrast the benefits and risks of chemoimmunotherapy with FCR versus bendamustine/rituximab (BR) as first-line therapy for fit patients with CLL.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCASH2014/4/CME.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Brad S Kahl, MD
Skoronski Chair of Lymphoma Research
Associate Professor
University of Wisconsin School of Medicine and Public Health
Associate Director for Clinical Research
UW Carbone Cancer Center
Madison, Wisconsin

Advisory Committee: Celgene Corporation, Genentech BioOncology, Millennium: The Takeda Oncology Company, Roche Laboratories Inc; Contracted Research: Genentech BioOncology, Roche Laboratories Inc.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Algeta US, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, Exelixis Inc, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Lilly, Medivation Inc, Merck, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Novocure, Onyx Pharmaceuticals Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc, Teva Oncology and VisionGate Inc.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

This activity is supported by educational grants from Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Seattle Genetics and Spectrum Pharmaceuticals Inc.

Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: March 2014
Expiration date: March 2015

5 MinuteJournalClub

POST-ASH Issue 4, 2014

To go directly to slides and commentary for this issue, **click here**.

Brad S Kahl, MD

Throughout a recent interview with investigator Dr Brad Kahl about the breathtaking developments in the treatment of chronic lymphocytic leukemia (CLL), my mind kept flashing back 24 hours to a similar recording session for our *Visiting Professors* audio series focused on the care of patients with a variety of advanced gastrointestinal cancers. One of the themes that regularly emerged during that discussion was the sense of desperation and hopelessness felt by patients and clinicians regarding the modest research advances that have recently taken place in that field. Coming from that concerning landscape, my conversation with Dr Kahl about CLL was a different story and hopefully the model for the future of oncology for patients, families and healthcare professionals.

Indeed, one might argue that in the short (50+ years) history of contemporary oncology the recent clinical research progress in CLL is unprecedented, as the confluence of a variety of research efforts has culminated in an abundance of new treatment options. To provide some insight into how emerging data will inform the integration of these exciting treatments into practice, here are Dr Kahl's perspectives on some of the most important CLL papers presented at the annual ASH meeting in New Orleans.

Chimeric antigen receptor (CAR) T-cell immunotherapy

A coming issue of this series will dive deeper into this extraordinary treatment that will eventually be studied in all B-cell cancers, but at ASH most of the data presented on this CAR-based T-cell therapy targeting CD19 were in CLL and acute lymphoblastic leukemia. The bottom line is that frequent, rapid and profound antitumor responses and a delayed cytokine release syndrome that requires a great deal of attention were observed. Stay tuned for full details.

Obinutuzumab

One of two recently approved agents in CLL (with more likely on the way), this type II anti-CD20 antibody was big news in the Big Easy as the plenary presentation of **the CLL11 trial** illustrated superior efficacy of obinutuzumab versus rituximab (R) in older patients and those with comorbidities receiving chlorambucil. Dr Kahl notes that clinicians must be aware of the potential for increased toxicity with this drug — particularly manageable infusion reactions mainly with the first treatment — but he believes the clear-cut benefit of obinutuzumab makes it difficult to use R in patients receiving chlorambucil.

Of course, an important related question is how this agent fits in with other chemotherapeutic regimens, and at ASH we saw data from **an ongoing Phase Ib trial** evaluating either fludarabine/cyclophosphamide (FC) or bendamustine (B) combined with obinutuzumab. The efficacy findings in this nonrandomized effort seemed similar to those historically observed with R, but this early report also described frequent infusion reactions and some myelosuppression. Dr Kahl believes that until further data become available, these combinations should not be used outside a trial setting.

FCR versus BR

Seems like eons ago when all we had to talk about was this important clinical question that was the subject of the **German CLL10 trial** in fit patients presented at ASH. Results from this much-awaited study demonstrated pretty much what most people expected and were already acting on in their practices — slightly greater efficacy in terms of complete response (CR) rates and progression-free survival (PFS) with FCR but considerably more toxicity, particularly in older patients. These data reinforce Dr Kahl's current nonprotocol approach to up-front treatment of CLL as follows:

- For younger patients, consider but do not insist on FCR, or, alternatively, administer BR.
- For older but not particularly frail patients (about age 60 to 75), usually opt for BR.
- For the difficult-to-define "very elderly," use chlorambucil/obinutuzumab.

Others will argue that few patients are too frail to receive bendamustine, but now that a new generation of novel agents has arrived, these issues are all being completely reconsidered anyhow.

Ibrutinib in relapsed/refractory (RR) CLL

Just approved in CLL, this Bruton tyrosine kinase inhibitor was the centerpiece of several Phase I-II ASH papers, all of which also continue to demonstrate high levels of activity, including in patients with del(17p) disease.

– **Ibrutinib alone**

A report from the NCI of the first 53 patients enrolled on **a Phase II trial** demonstrated that two thirds of these individuals responded. Most of the remaining patients responded in nodes and other sites but with increasing rather than decreasing white blood cell counts. This lymphocytosis is observed with a variety of the new small B-cell receptor inhibitors and may be part of a demargination syndrome with cells being discharged into circulation from the protected microenvironment of the marrow, spleen and the lymph nodes. With time the white counts eventually decrease — often normalizing — and this has led to a special response classification of "partial response with lymphocytosis" that occurred in 28% of 47 evaluable patients for an overall response rate of 94%. Dr Kahl views these cases as essentially CRs because the circulating cells eventually die, and it's not clear if abrogating this phenomenon with another antineoplastic agent like R or chemotherapy adds to long-term treatment benefit.

– **Ibrutinib with R**

Thirty-eight of 40 (95%) patients on **this Phase II trial** experienced objective responses, and Dr Kahl views this higher rate compared to ibrutinib monotherapy as mainly the result of counteracting the initial lymphocytosis and notes it remains to be seen if this will affect long-term outcome and survival. An ongoing randomized Phase II trial in RR CLL evaluating ibrutinib alone or with R will hopefully provide part of the answer to this important question.

– **Ibrutinib with BR**

Although 93% of 30 patients responded in **this Phase Ib trial**, as per Dr Kahl it's not clear that bendamustine is adding anything to ibrutinib or as previously stated that R provides long-term benefit. Dr Kahl, like most or all investigators, is currently using ibrutinib in relapsed CLL as per the indication, but it will be interesting to see how this evolves as more data accumulate on earlier use, particularly in cases with adverse cytogenetic factors and for the elderly.

Idelalisib

Another major story at ASH was a "late breaker" and *New England Journal* publication (along with the CLL11 obinutuzumab trial) detailing the results from **a Phase III trial** evaluating R with or without this PI3 kinase-delta inhibitor in 220 patients with relapsed disease who were not candidates for chemotherapy (median age 71). An overwhelming advantage was seen in the combination arm — 81% versus 13% overall response rate and marked improvement in PFS (HR = 0.15) and overall survival (HR = 0.28), both statistically significant. However, Dr Kahl wonders if the comparison to R, a notoriously ineffective monotherapy in CLL, will be enough to elicit FDA approval.

ABT-199

This fascinating small molecule inhibits BCL-2, which is frequently overexpressed in lymphoid cancers and a cause of dysregulation of apoptosis. While ABT-199 may still be in need of a name, it is quickly gaining a great deal of attention, and according to Dr Kahl the most significant problem may be that it "works too well," with an overall response rate of 84% among 56 evaluable patients and similar response rates irrespective of del(17p) status. Specifically, the rapid and profound antitumor activity associated with the agent frequently results in tumor lysis syndrome. As such, **an ongoing Phase I study** presented at ASH attempted to define the optimal dosing strategy to prevent this worrisome side effect. Regardless, Dr Kahl believes that ABT-199 will eventually prove to be as efficacious in CLL as ibrutinib — the agent he currently feels is the most effective available for the disease.

From the perspective of the general oncologist, the deluge of new agents and therapies in CLL is likely to result in frequently changing clinical algorithms during the next few years as trials evaluate various sequences, combinations and predictive factors. It seems inevitable that the outcomes of patients will improve significantly, and the best-case scenario is cure or a functional cure with normal life expectancy as with chronic myelogenous leukemia. It remains to be seen whether this type of exciting clinical paradigm will enter mainstream oncology in the future and include the many patients with GI cancers and other solid tumors who currently face much more limited options.

Next on this ASH review series, Dr Rafael Fonseca talks about new therapies in multiple myeloma, with more on the recently approved agents carfilzomib and pomalidomide, and a wave of promising other molecules, including several monoclonal antibodies attempting to become the "rituximab of myeloma."

Neil Love, MD
Research To Practice
Miami, Florida

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

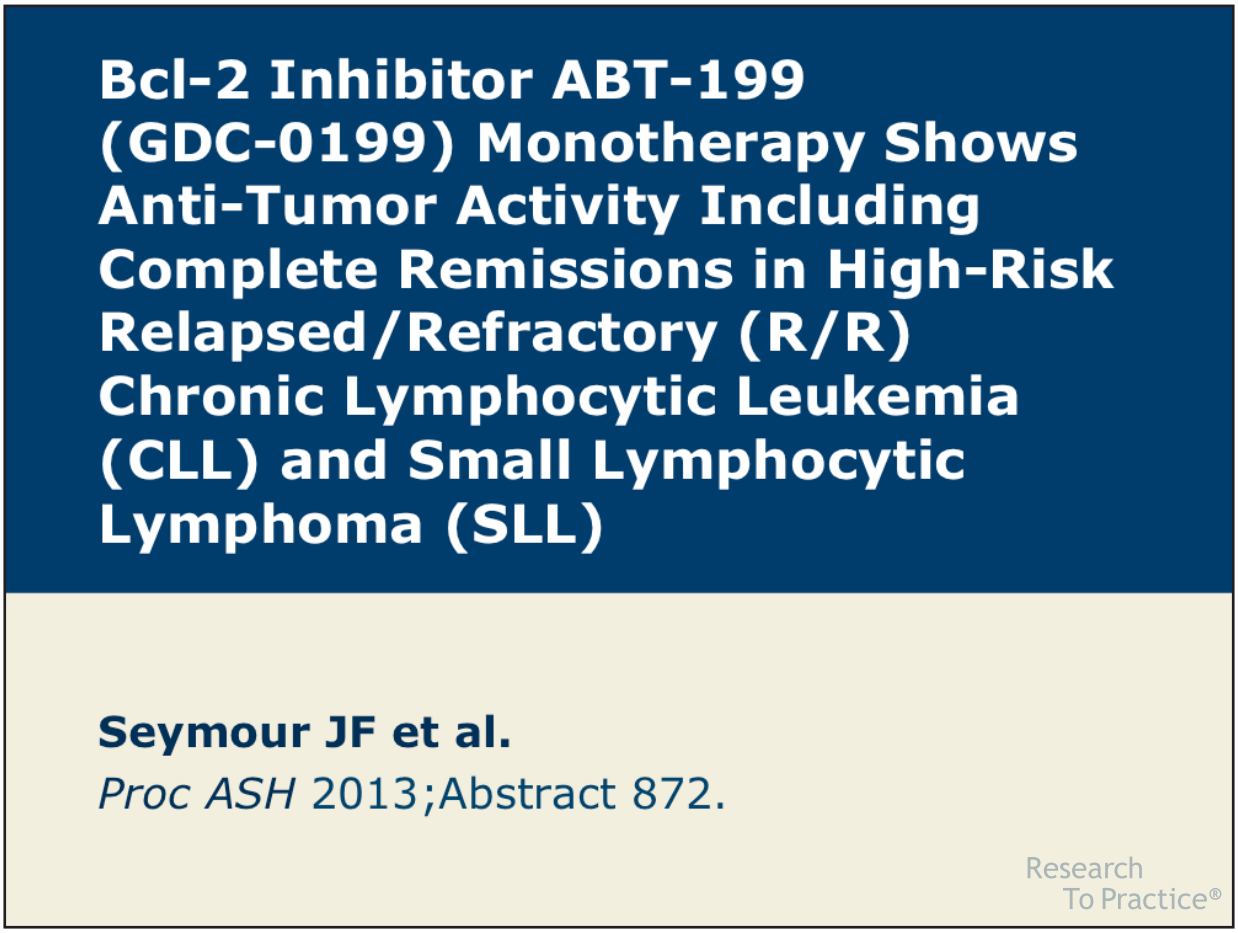
This activity is supported by educational grants from Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Seattle Genetics and Spectrum Pharmaceuticals Inc.

BCL-2 Inhibitor ABT-199 Monotherapy for High-Risk Relapsed/Refractory CLL or SLL

Presentation discussed in this issue

Seymour JF et al. **Bcl-2 inhibitor ABT-199 (GDC-0199) monotherapy shows anti-tumor activity including complete remissions in high-risk relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).** *Proc ASH* 2013;**Abstract 872**.

Slides from a presentation at ASH 2013 and transcribed comments from a recent interview with Brad S Kahl, MD (2/13/14)



Background

- The intrinsic apoptotic pathway is often dysregulated in relapsed CLL/SLL due to a deficiency in proapoptotic proteins and the overexpression of antiapoptotic proteins such as Bcl-2.
- ABT-199 is a selective, potent, orally bioavailable, small molecule Bcl-2 inhibitor that can trigger apoptosis in vitro, even in CLL cells harboring the del(17p) chromosomal abnormality.
- Rapid tumor lytic activity in a small number of patients with refractory CLL has been demonstrated with ABT-199 (*Nat Med* 2013;19:202).
- **Study objective:** To evaluate the safety, pharmacokinetics, maximum tolerated dose and preliminary efficacy of ABT-199 in relapsed/refractory CLL or SLL.

Seymour JF et al. *Proc ASH* 2013;Abstract 872.

Research To Practice®

Ongoing Phase I Study Design (NCT01328626)

Target accrual (n = 211*)

Relapsed/refractory CLL or SLL
No prior autologous or allogeneic stem cell transplant

→

Dose escalation

ABT-199
Single dose, wk1 d-3 or d-7
Continuous once-daily dosing starting wk1 d1 until PD†

* As of July 4, 2013, 56 patients were enrolled in cohorts at 150-mg to 1,200-mg doses
† Modifications were made to the dose-escalation scheme, tumor lysis syndrome (TLS) prophylaxis and monitoring schedule after TLS was observed in some patients

Primary endpoints: Safety, pharmacokinetics, maximum tolerated dose, recommended Phase II dose

Secondary endpoints include: Preliminary efficacy, biomarkers of response

Seymour JF et al. *Proc ASH* 2013;Abstract 872; www.clinicaltrials.gov, February 2014.

Baseline Characteristics

Response	All pts (n = 56)	del(17p)* (n = 17)	F-refractory* (n = 18)
Median age	67 years	69 years	66 years
Bulky disease ≥5 cm ≥10 cm	 50% 14%	 35% 0%	 56% 22%
Median lymphocyte count	4.9 x 10^9/L	5.9 x 10^9/L	4.5 x 10^9/L
Median no. of prior therapies (range)	4 (1-10)	4 (2-9)	5 (1-10)
Median time on study	10.0 mo	9.7 mo	10.4 mo

F = fludarabine

* 6 patients had both del(17p) and F-refractory disease

- 12 of 27 patients (44%) had beta-2 microglobulin levels >3 mg/L
- 20 of 24 patients (83%) had IGVH-unmutated status

Seymour JF et al. *Proc ASH* 2013;Abstract 872 (abstract only).

Research To Practice®

Response Rates

Response	All pts (n = 56)	del(17p) (n = 17)	F-refractory (n = 18)
Overall response rate	84%	82%	78%
Complete remission/ complete remission with incomplete blood count recovery (CR/CRi)	21%	12%	17%
Partial remission*	63%	71%	61%
Stable disease	7%	6%	6%
Progressive disease	2%	6%	—

* 3 patients had confirmatory CT imaging assessments at less than an 8-week interval (5, 6 and 7 weeks)

Seymour JF et al. *Proc ASH* 2013;Abstract 872 (abstract only).

Research To Practice®

Minimal Residual Disease (MRD) Assessment

- In patients achieving CR/CRi, MRD was quantified with 4-color flow cytometry (aiming to analyze >200,000 nucleated cells).
- Patients with evaluable results (n = 8):
  - No detectable MRD: n = 4 (2 with suboptimal cells analyzed)
  - Low-level MRD: n = 4
- Of the patients who had no detectable MRD, 1 had del(17p) and F-refractory disease and 2 had F-refractory disease.

Seymour JF et al. *Proc ASH* 2013;Abstract 872 (abstract only).

Research To Practice®

Adverse Events (AEs)

Grade 3/4 AE (≥4 pts)	n = 56
Neutropenia	41%
TLS	11%
Thrombocytopenia	10%
Hyperglycemia	10%
Anemia	7%
Febrile neutropenia	7%

- Most common AEs of all grades (≥25% of patients): Diarrhea (46%), neutropenia (43%), fatigue (34%), upper respiratory tract infection (29%) and cough (25%)
- 7 dose-limiting toxicities: 5 cases of TLS (1 G3 laboratory based at 50 mg; 1 G4 clinical AE at 50 mg; 1 G3 laboratory based at 100 mg and 2 at 200 mg), 1 G4 neutropenia (600 mg) and sudden death (1,200 mg) in the setting of G4 (clinical) TLS.

Seymour JF et al. *Proc ASH* 2013;Abstract 872 (abstract only).

Research To Practice®

Author Conclusions

- ABT-199 showed activity in patients with relapsed/refractory CLL with a response rate of 84% for the study population, including a 21% rate of CR/CRi.
- Similar efficacy was seen in patients with high-risk CLL, with a response rate of 82% in patients with del(17p) and 78% in those with F-refractory disease.
- 3 of 4 patients who had no detectable MRD and achieved a CR/CRi were patients with high-risk disease.
- This study is continuing enrollment using a revised dosing schedule designed to reduce the identified risk of TLS.
- A Phase II monotherapy study in patients with relapsed/refractory CLL with del(17p) has commenced (NCT01889186), and combination studies are ongoing with either rituximab (NCT02005471) or obinutuzumab (NCT01685892) in patients with relapsed/refractory CLL.

Research To Practice®

Seymour JF et al. *Proc ASH* 2013;Abstract 872 (abstract only).

Investigator Commentary: ABT-199 Demonstrates Antitumor Activity in High-Risk, Relapsed/Refractory CLL and SLL

Bcl-2 causes dysregulation of apoptosisis and is overexpressed in a variety of lymphoid cancers. The Bcl-2 inhibitor ABT-199 has overcome the problem of thrombocytopenia encountered with prior inhibitors in the same class. It is orally bioavailable and well absorbed.

Patients in this ongoing Phase I study received a range of doses of ABT-199 from 150 mg to 1,200 mg per day. Problems with TLS occurred, and 1 patient receiving the 1,200-mg dose died. The study had to be put on hold and redesigned with a lower dosing scheme and close monitoring.

Patients must start with a low dose of ABT-199 and undergo a carefully monitored dose escalation. It can take 4 to 6 weeks to reach the target dose, which is 400 mg per day for CLL. TLS can be an issue with this agent but is manageable. Overall the drug is well tolerated.

The efficacy of ABT-199 in CLL is amazing. It is as good as ibrutinib, which is the best drug in CLL. The overall response rate is 84% and is similar for patients with del(17p) or those with fludarabine-refractory disease. I'm very optimistic about the future of ABT-199 in CLL.

Interview with Brad S Kahl, MD, February 13, 2014

Research To Practice®