



*POST-ASH* Issue 2, 2016

# Venetoclax Alone or as Combination Therapy for CLL

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## 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. 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 unmatched 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 novel agents and therapeutic options for the treatment of newly diagnosed and relapsed/refractory chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL) 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

- Appraise recent clinical research findings on the efficacy and safety of venetoclax alone or in combination for patients with CLL and FL.
- Compare the risks and benefits associated with the Bruton tyrosine kinase inhibitors ibrutinib and acalabrutinib for the treatment of CLL.
- Evaluate the activity and tolerability of obinutuzumab/bendamustine for patients with previously untreated CLL.
- Recall recent data on the activity of pembrolizumab in the treatment of relapsed/refractory CLL, including for patients with Richter's transformation.
- Assess the safety of idelalisib in the front-line treatment of CLL.

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

Jeff Sharman, MD  
Director of Research, Willamette Valley Cancer Institute  
Medical Director of Hematology Research  
The US Oncology Network  
Eugene, Oregon

Advisory Committee and Consulting Agreements: Celgene Corporation, Genentech BioOncology, Gilead Sciences Inc, Pharmacyclics Inc; Contracted Research: Celgene Corporation, Cephalon Inc, Genentech BioOncology, Gilead Sciences Inc, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals, an Amgen subsidiary, Pharmacyclics Inc.

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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 2016

Expiration date: March 2017

To go directly to slides and commentary for this issue, [click here](#).

Less than 2 weeks ago, in a historic act that will instantly affect the treatment of one of the most common hematologic cancers in general oncology practice, the FDA broadened the first-line indication of ibrutinib to now include patients both with and *without* 17p-deleted chronic lymphocytic leukemia (CLL). This landmark event is just part of an unprecedented explosion of new data and treatment options that have redefined the management of this disease over the past few years.

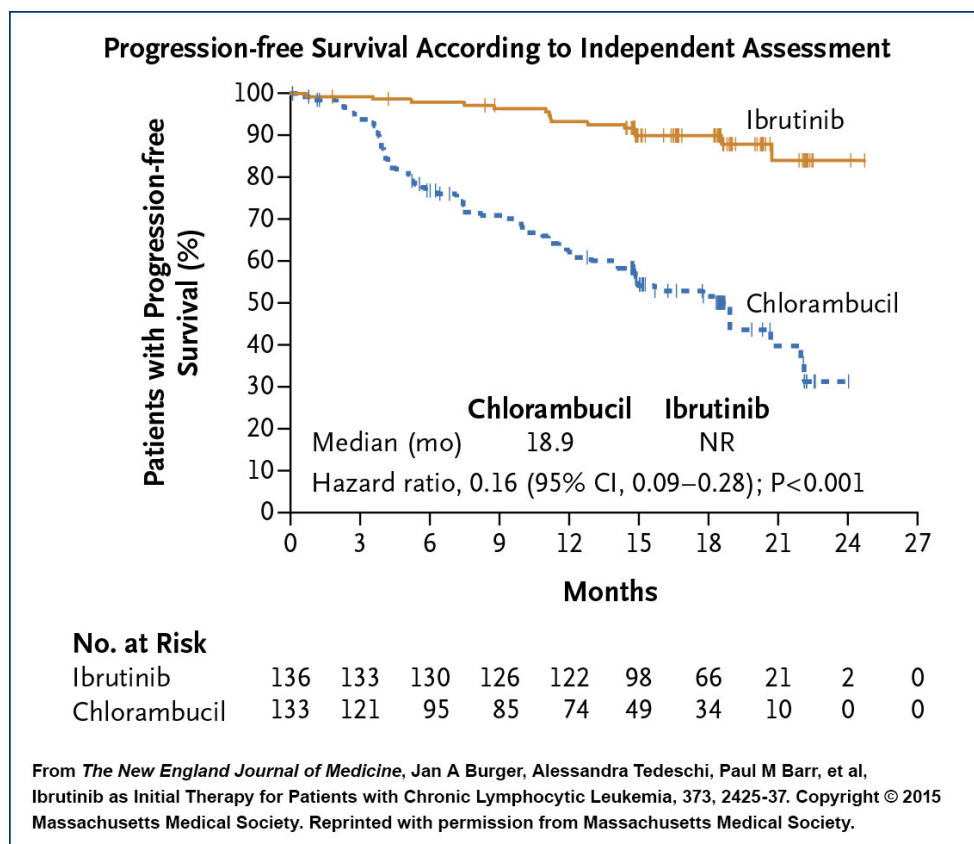


**Jeff Sharman, MD**

One of the many investigators in this worldwide effort is Dr Jeff Sharman, who first at Stanford and now in Springfield, Oregon has gained extensive practical experience working with many of the novel agents that are now part of current algorithms. I met with Jeff to learn about his perspectives — from both a clinical and a research standpoint — on relevant CLL and non-Hodgkin lymphoma data sets presented at the December ASH meeting and how these add to the rapidly evolving therapeutic paradigms in these cancers ([click for the interview](#)). Below find a summary of this conversation along with slides detailing the key findings from the ASH papers ([click to review](#)).

### **RESONATE-2: Ibrutinib versus chlorambucil in untreated CLL**

In what might be compared to a matchup between the Green Bay Packers and my alma mater, Milford Mill High School, this randomized Phase III trial not surprisingly demonstrated the clear-cut superiority of the Bruton tyrosine kinase (BTK) inhibitor, with spectacular progression-free survival (PFS) and overall survival (OS) HRs of 0.16 for both endpoints. Although the trial focused on patients older than 65, the design and the results did not compel the FDA to tie an age stipulation to the recent approval expansion. In addition, ibrutinib had an acceptable safety profile, with the majority of adverse events being Grade 1 and a lower rate of treatment discontinuation due to toxicity compared to chlorambucil (9% versus 23%). As such, many, including Dr Sharman, believe ibrutinib will become the standard first-line treatment for most patients with CLL. He pointed out that the one exception might be younger patients with IgVH-mutated disease without high-risk FISH findings in whom a chemoimmunotherapy regimen like fludarabine/cyclophosphamide/rituximab (FCR) could potentially result in a prolonged remission or cure without the need for continuous treatment.



In discussing how the indefinite use of up-front ibrutinib may affect clinical practice, Dr Sharman focused on the need to pay even greater attention to the variety of treatment-related complications and potential adverse drug-drug interactions (discussed in another ASH report) that might lead to temporary discontinuation of this generally well-tolerated therapy. His concern in this regard stems from recent research demonstrating that treatment interruption for even 8 days has been associated with a reduction in PFS, a cautionary tale about the potential challenges of administering this or almost any agent indefinitely.

### **Acalabrutinib (acala-B): A better BTK inhibitor?**

The extraordinary efficacy of acala-B might or might not exceed that of ibrutinib, but perhaps of equal importance is the hope that the safety profile may be superior, with early-onset headaches being the most common problem rather than the arthralgias, bruising, bleeding and atrial fibrillation observed with ibrutinib. In a Phase I/II trial of 60 evaluable patients with relapsed disease, responses were observed in 95% of patients, including all 18 with del(17p). A head-to-head Phase III trial will compare these relatively close cousins, but Dr Sharman believes this is another novel agent churning its way steadily toward approval.

### **Idelalisib in CLL**

In one of the highlights of the late-breaking abstract session, Dr Andrew Zelenetz presented results of a Phase III trial evaluating bendamustine/rituximab (BR) alone or with idelalisib in relapsed/refractory (R/R) disease. The study, which was stopped early

based on “overwhelming efficacy,” demonstrated an impressive improvement in both PFS (HR 0.33) and OS (HR 0.55), and the findings were consistent for patients with or without high-risk features. Although Dr Sharman questions whether bendamustine really adds much to idelalisib/rituximab, he does consider BR/idelalisib a rational option in the R/R setting.

Importantly, another study at ASH — idelalisib up front combined with ofatumumab — revealed an overall response rate (ORR) of 100% among 24 patients but an excess of immune-related adverse events such as hepatitis, pneumonitis and colitis. Dr Sharman believes these toxicities are likely related to the drug’s inhibition of regulatory T cells and explained that the lower frequency of idelalisib-related immune toxicity in the R/R setting may be the result of what he calls “immuno-plegia” as a consequence of prior therapies such as FCR. As a direct result of these new toxicity findings, just yesterday the FDA announced that 6 ongoing combination trials involving idelalisib and a number of other anti-cancer agents had been stopped.

### **Venetoclax in CLL**

Although it is still in clinical development, the emergence of this highly effective Bcl-2 inhibitor represents another gigantic recent CLL advancement, and in Orlando we saw more impressive data with this agent in del(17p) disease with an ORR of 79.4% among 107 patients with R/R disease. We were also treated to some encouraging findings with combination regimens that included bendamustine, rituximab and obinutuzumab (obin) administered prior to, after or with the Bcl-2 inhibitor.

The FDA has now bestowed not 1 but 2 breakthrough therapy designations upon the drug in CLL, and Dr Sharman believes that the overwhelming database supporting the useful clinical role of this agent will likely lead to its approval this year. However, he and others remain somewhat concerned about the potential for tumor lysis syndrome (TLS), which was observed in early trials, and would like to see specific recommendations emerge for how to prevent or manage this phenomenon. In that regard, he believes that we will likely be assessing pretreatment tumor burden and renal function to determine baseline risk for TLS and then aggressively monitoring or even hospitalizing select patients. With that being said, the availability of another profoundly effective agent with a totally different mechanism of action has the entire CLL investigator community wide eyed with excitement over the possibility of long-term or lifelong disease control.

### **Obinutuzumab in CLL**

It will be interesting to see how the role of this novel anti-CD20 antibody evolves with ibrutinib rapidly moving in on its indicated turf and the current/emerging treatment roster loaded with other novel small agents. Regardless, many believe this drug has good activity in CLL (likely more than rituximab) and for that reason were excited to determine how it would fare in combination with bendamustine. At ASH we saw more

from the single-arm GREEN study of bendamustine/obin in untreated and R/R disease demonstrating encouraging efficacy and acceptable toxicity with some concerns about TLS and neutropenia. In the current analysis of 158 patients with previously untreated disease, the bendamustine/obin combination yielded a complete response rate of 32.3%, with minimal residual disease negativity in blood and bone marrow of 58.9% and 28.5%, respectively. Despite these data, Dr Sharman believes the regimen is not yet ready for clinical practice in CLL. It is worth noting that on February 26 of this year the FDA approved bendamustine/obin followed by obin maintenance for patients with *follicular lymphoma (FL)* who did not respond to a rituximab-containing regimen.

### **Pembrolizumab in CLL with Richter's transformation (RT)**

RT occurs in approximately 2% to 10% of all CLL cases, and Dr Sharman commented that recently 2 patients in his practice died within 72 hours of diagnosis, in keeping with the often rapidly progressive course. In this preliminary ASH report of 5 patients with RT, 4 had mostly rapid and deep responses after receiving this anti-PD-1 antibody alone. Although it is clearly early days, Jeff found the findings so encouraging that he recently initiated treatment outside a trial setting with this agent in a patient with RT.

### **ASH disappointments in indolent lymphoma (ibrutinib, venetoclax)**

With all the excitement in CLL, the ASH papers focused on indolent lymphomas were a bit underwhelming. In particular 2 studies in FL **combining ibrutinib with either rituximab or rituximab/lenalidomide** (R<sup>2</sup>) along with a **couple of Phase I trials** of venetoclax alone or with BR failed to inspire Dr Sharman, particularly when he considers how active idelalisib has been in this setting. He did find intriguing the significant activity observed with the Bcl-2 inhibitor in mantle-cell lymphoma, perhaps related to its biologic and therapeutic similarity to CLL.

Next on this series, Dr Michelle Fanale comments on other lymphoma papers from ASH, including more on the exciting findings now being reported with the use of checkpoint inhibitors in Hodgkin lymphoma.

Neil Love, MD

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Miami, Florida

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This activity is supported by educational grants from Celgene Corporation, CTI BioPharma Corp/ Baxalta Inc, Jazz Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Seattle Genetics and Takeda Oncology.

# Venetoclax Alone or as Combination Therapy for CLL

## Presentations discussed in this issue

Stilgenbauer S et al. **Venetoclax (ABT-199/GDC-0199) monotherapy induces deep remissions, including complete remission and undetectable MRD, in ultra-high risk relapsed/refractory chronic lymphocytic leukemia with 17p deletion: Results of the pivotal international Phase 2 study.** *Proc ASH 2015*; [Abstract LBA-6](#).

Salles GA et al. **Updated safety and preliminary efficacy data from a Phase 1b study combining venetoclax (GDC-0199, ABT-199) with bendamustine/rituximab in patients with relapsed/refractory or previously untreated chronic lymphocytic leukemia.** *Proc ASH 2015*; [Abstract 829](#).

Ma S et al. **Deep and durable responses following venetoclax (ABT-199/GDC-0199) combined with rituximab in patients with relapsed/refractory chronic lymphocytic leukemia: Results from a Phase 1b study.** *Proc ASH 2015*; [Abstract 830](#).

Flinn IW et al. **Safety and efficacy of a combination of venetoclax (GDC-0199/ABT-199) and obinutuzumab in patients with relapsed/refractory or previously untreated chronic lymphocytic leukemia – Results from a Phase 1b study (GP28331).** *Proc ASH 2015*; [Abstract 494](#).

**Slides from presentations at ASH 2015 and transcribed comments from a recent interview with Jeff Sharman, MD (2/9/16)**

**Venetoclax (ABT-199/GDC-0199) Monotherapy Induces Deep Remissions, Including Complete Remission and Undetectable MRD, in Ultra-High Risk Relapsed/Refractory Chronic Lymphocytic Leukemia with 17p Deletion: Results of the Pivotal International Phase 2 Study<sup>1</sup>**

**Updated Safety and Preliminary Efficacy Data from a Phase 1b Study Combining Venetoclax (GDC-0199, ABT-199) with Bendamustine/Rituximab in Patients with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukemia<sup>2</sup>**

<sup>1</sup> **Stilgenbauer S et al.**  
*Proc ASH 2015*; Abstract LBA-6.

<sup>2</sup> **Salles GA et al.**  
*Proc ASH 2015*; Abstract 829.

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## Deep and Durable Responses Following Venetoclax (ABT-199/GDC-0199) Combined with Rituximab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Results from a Phase 1b Study<sup>3</sup>

## Safety and Efficacy of a Combination of Venetoclax (GDC-0199/ABT-199) and Obinutuzumab in Patients with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukemia — Results from a Phase 1b Study (GP28331)<sup>4</sup>

<sup>3</sup> Ma S et al.

*Proc ASH 2015;Abstract 830.*

<sup>4</sup> Flinn IW et al.

*Proc ASH 2015;Abstract 494.*

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## Venetoclax (VEN) Monotherapy in Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL) with Del(17p)

- Phase II study of VEN monotherapy
- N = 107 patients with R/R CLL and del(17p)
- **Primary study endpoint:** Overall response rate (ORR) by independent review committee (IRC)

Response (IRC assessed)	N = 107
ORR	79.4%
CR or CRi	7.5%
nPR/PR	72%
Survival rate (12 mo)	
Progression-free survival (PFS)	72%
Overall survival (OS)	86.7%

CR = complete remission; CRi = CR with incomplete bone marrow recovery; nPR = nodular partial remission; PR = partial remission

Stilgenbauer S et al. *Proc ASH 2015;Abstract LBA-6.*

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## VEN in R/R CLL with Del(17p): Conclusions

- VEN monotherapy achieved deep responses with acceptable toxicity in this ultrahigh-risk population with R/R del(17p) CLL:
  - More than 10% IRC-confirmed CR, CRi or nPR
  - Minimal residual disease (MRD) negativity observed in more than 20% of responders
- Favorable risk-benefit profile:
  - Risk of tumor lysis syndrome (TLS) effectively mitigated with no clinical TLS
  - Incidence of neutropenia (43%) and infection (72%) similar to front-line chemoimmunotherapy

Stilgenbauer S et al. *Proc ASH* 2015;Abstract LBA-6.

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## VEN with Bendamustine (B)/ Rituximab (R) in Untreated or R/R CLL

- Ongoing Phase Ib study of VEN with B/R or B/obinutuzumab
  - 2 schedules tested: VEN introduced first or B/R or B/obinutuzumab introduced first, both with gradual VEN dose increase
- N = 30 patients with untreated or R/R CLL
- **Primary endpoints:** Maximum tolerated dose, safety of VEN with B/R

Adverse event (AE)	Grade ≥3	Serious AE
Neutropenia	17 (57%)	1 (3%)
Thrombocytopenia	5 (17%)	0 (0)
Diarrhea	3 (10%)	0 (0)
Hypertension	2 (7%)	0 (0)
TLS	0 (0)	0 (0)

Salles GA et al. *Proc ASH* 2015;Abstract 829.

## VEN with B/R in CLL: Conclusions

- Daily VEN 400 mg can be safely combined with B/R in patients with R/R CLL using either administration schedule (VEN or B/R first), with no dose-limiting toxicities at this dose.
- No TLS was observed with either administration schedule despite many patients being at medium (53%) or high (33%) risk for TLS.
- VEN + B/R is associated with frequent hematologic toxicity, which appears to be manageable in most cases.
- Early response and MRD data are promising:
  - Of 22 patients with R/R CLL evaluated, 100% responded
  - Overall, 70% of patients achieved MRD negativity

Salles GA et al. *Proc ASH* 2015;Abstract 829.

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## VEN/R in CLL

- Phase Ib study of VEN/R in 5 dose-escalation cohorts (200-600 mg/d VEN) and a safety expansion cohort (400 mg/d VEN)
  - VEN dosing was continuous
- N = 49 patients with R/R CLL/small lymphocytic leukemia (SLL)
- **Study aims:** Safety, MRD status, survival, response
  - Cohorts combined for analyses
- Two-year PFS: 83%; 2-year OS: 94%

	All (N = 49)	Del(17p) Mut(TP53) (n = 15)	IGHV unmut (n = 19)	Fludarabine refractory (n = 9)	R refractory (n = 14)
ORR	86%	87%	84%	56%	64%
CR/CRi	47%	47%	47%	44%	29%
PR/nPR	39%	40%	37%	11%	36%

Ma S et al. *Proc ASH* 2015;Abstract 830.

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## VEN/R in CLL: Conclusions

- VEN/R induces a high rate of deep and durable responses independent of adverse prognostic characteristics:
  - ORR: 86%; CR/CRi: 47%
  - MRD negativity in bone marrow: 55%
  - All patients with MRD-negative disease maintained their response
  - Remission off all therapy has been maintained in all patients achieving MRD-negative CR
- The high rate of MRD negativity is an encouraging step toward prolonged PFS and durable elimination of CLL/SLL.
- One case of treatment-emergent TLS leading to death was reported; No fatal TLS events occurred after a protocol modification aimed at TLS risk management and prophylaxis.
- VEN/R is being evaluated versus B/R in the Phase III MURANO trial for patients with R/R CLL (NCT02005471).

Ma S et al. *Proc ASH* 2015;Abstract 830.

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## VEN with Obinutuzumab (G) in CLL

- Phase Ib study of VEN combined with G on 2 different dose schedules
- N = 32 patients with treatment-naïve (TN) or R/R CLL
  - TN (n = 6): 6 cycles of VEN + G → VEN x 6 mo
  - R/R (n = 26): 6 cycles of VEN + G → VEN until disease progression
- **Primary endpoint:** Maximum tolerated dose

Serious AEs in ≥2 patients	N = 32
Hyperphosphatemia	3 (9.4%)
TLS	2 (6.3%)
Pyrexia	2 (6.3%)

Flinn IW et al. *Proc ASH* 2015;Abstract 494.

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## VEN with G in CLL: Conclusions

- Preliminary data suggest that VEN + G can be safely administered to patients with CLL, with no difference in tolerability between patients with TN and R/R disease.
- AEs appear to be manageable, and the data suggest that TLS prophylaxis measures are appropriate.
- Preliminary efficacy data demonstrate that all patients who received VEN + G responded.
  - For patients with R/R CLL after 3 cycles of therapy: CR/CRi n = 4; PR n = 17 (3 improved to CR/CRi after 6 cycles of therapy)
- An expansion phase is planned using a 400-mg/d dose of VEN for TN and R/R disease.
- Evaluation of VEN + G for patients with CLL continues in the ongoing Phase III CLL14 trial.

Flinn IW et al. *Proc ASH 2015*;Abstract 494.

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### **Investigator Commentary: Efficacy and Safety of Phase Ib or II Studies of Venetoclax Alone or in Combination Therapy for Untreated or R/R CLL**

Multiple studies presented this year at the American Society of Hematology Annual Meeting further characterize the efficacy of venetoclax in CLL. This exciting agent has demonstrated some of the most robust activity observed in patients with CLL. Venetoclax is expected to gain FDA approval in 2016. The initial indication will likely focus on those patients with 17p deletion.

Perhaps the greatest danger associated with this agent is tumor lysis syndrome (TLS). Practitioners who are unfamiliar with venetoclax need to become aware of the risks associated with its use. Early in the development of this molecule 2 patients died of TLS, and this led to a modified dose-escalation approach to treatment. Despite these modifications, chemical tumor lysis (lacking clinical complications) has been observed in approximately 5% of patients. The risk of TLS increases with a lymphocyte count in excess of 25,000 and with lymph nodes larger than 5 centimeters.

*Continued*

### **Investigator Commentary: Efficacy and Safety of Phase Ib or II Studies of Venetoclax Alone or in Combination Therapy for Untreated or R/R CLL**

Using these 2 characteristics to assess risk, approximately one quarter of patients are considered to be at low risk, half are considered to be at intermediate risk (having 1 of the risk factors) and one quarter of patients are deemed to be at high risk. Furthermore, creatinine clearance less than 80 mL/min further increases the risk for TLS. After the initial dose of this drug and every subsequent dose escalation, repeat evaluation for TLS 6 to 8 hours after administration is encouraged. It is anticipated that many patients starting venetoclax will need to receive it in the hospital for adequate monitoring.

Among the patients at high risk with 17p deletion, 107 patients received the drug. The response rate was approximately 80%, with more than 20% of patients with heavily pretreated, high-risk disease achieving MRD negative status in the peripheral blood. A few of these even attained MRD-negativity in the bone marrow, indicating an exceptionally high rate of deep responses. The median time to first response was only several weeks.

*Continued*

### **Investigator Commentary: Efficacy and Safety of Phase Ib or II Studies of Venetoclax Alone or in Combination Therapy for Untreated or R/R CLL**

Although many drugs in oncology are moved into combination strategies when they lack single-agent activity, venetoclax is being partnered with other drugs such as bendamustine, rituximab or obinutuzumab for the purpose of debulking the CLL prior to initiation of Bcl-2 inhibitors. This may reduce the risk of TLS.

This exciting agent will play an increasing role in the management of CLL, and multiple ongoing studies will help to define its proper timing and use.

***Interview with Jeff Sharman, MD, February 9, 2016***

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