5 Minute JournalClub

POST-ASH Issue 2, 2013

The Btk Inhibitor Ibrutinib (PCI-32765) Alone and in Combination with Rituximab for CLL or SLL

For more visit ResearchToPractice.com/5MJCASH2013

Research To Practice®

CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows 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 with lenalidomide/rituximab for patients with untreated indolent lymphoma and, where appropriate, counsel patients regarding participation in ongoing pivotal trials assessing this strategy.
- Evaluate the early efficacy and safety data with the anti-PD-1 monoclonal antibody pidilizumab (CT-011) for patients with relapsed/refractory FL.
- Assess the benefits and risks of novel therapeutic approaches — PI3 kinase inhibitors, Btk inhibitors and chimeric antigen receptor T cells — under investigation in B-cell neoplasms and, where appropriate, facilitate patient access to ongoing trials of these agents.
- Optimize outcomes for elderly patients with CLL through the application of emerging clinical research data.

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 1.75 *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/5MJCASH2013/2/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:

Bruce D Cheson, MD
Professor of Medicine
Deputy Chief, Division of Hematology-Oncology
Head of Hematology
Georgetown University Hospital
Lombardi Comprehensive Cancer Center
Washington, DC

Advisory Committee: Celgene Corporation, Cephalon Inc, Gilead Sciences Inc, Mundipharma International Limited, Onyx Pharmaceuticals Inc, Pharmacyclics Inc, Sanofi; Consulting Agreements: Celgene Corporation, Cephalon Inc, Genentech BioOncology, Mundipharma International Limited.

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, Cephalon Inc, Genentech BioOncology, Millennium: The Takeda Oncology Company, Roche Laboratories Inc; Contracted Research: Abbott Laboratories, Cephalon Inc, Genentech BioOncology.

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, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, 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, EMD Serono Inc, Foundation Medicine Inc, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Lilly USA LLC, Medivation Inc, Merck, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc and Teva Oncology.

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 Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva Oncology.

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: February 2013
Expiration date: February 2014

5 MinuteJournalClub

POST-ASH Issue 2, 2013

ASH 2012 and the postrituximab era of new biologic treatments for B-cell neoplasms

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

Since the late 1990s rituximab (R) has been the major biologic agent integrated into management of B-cell cancers. However, these days some of the most cautious, evidence-based investigators are having a hard time hiding their enthusiasm for an array of emerging novel agents that are shaking up the non-Hodgkin lymphoma (NHL)/ chronic lymphocytic leukemia (CLL) research database. On this second issue of our 7-part ASH highlights series, we profile several promising new strategies, including a few that MD Anderson's Dr Hagop Kantarjian believes may soon lead to CML-like long-term disease control in CLL. Here's an overview of what we learned in Atlanta:

1. Small-molecule B-cell receptor inhibitors: Ibrutinib (Ib) and idelalisib (GS-1101)

These oral, relatively nontoxic agents interfere with the B-cell receptor signaling pathway and have intriguing activity in CLL, follicular lymphoma (FL) and mantle-cell lymphoma (MCL). Perhaps the greatest excitement surrounds Ib, an inhibitor of Bruton's tyrosine kinase, which is critical for proliferation and survival in most B-cell tumors. Ib was the subject of **2 spectacular CLL ASH papers**. The first was a Phase I-II monotherapy study of 116 patients that resulted in response rates Dr Bruce Cheson called "phenomenal" and exceeded 65% overall, including 12 of 24 patients with 17p and 11q deletions.

The second major related paper was a Phase II study evaluating the combination of Ib and R in 40 patients with previously treated high-risk CLL. I was struck by the title of the abstract, which states that this combination had "profound" activity. Given that description, the eye-popping **waterfall plots**, which pretty much all point south and included 13 patients with del 17p, were not that surprising. A highlight of this paper was the discussion of a patient who had primary resistance to FCR then hyper-CVAD and a number of other therapies but achieved a CR with Ib/R.

With regard to idelalisib, at ASH we saw findings from **a Phase I study** evaluating this PI3 kinase delta inhibitor combined with R and/or bendamustine (B) in 52 patients with relapsed/refractory (RR) CLL. PI3K delta is thought to drive proliferation and survival of malignant B cells, and as in many Phase I studies in this era of molecular-targeted treatment, most (about 80%) of the patients responded despite extensive prior treatments, including B and R. This well-tolerated combination approach is now being tested in Phase III trials.

2. Lenalidomide (len)

The first issue of this ASH series profiled immunomodulatory agents in multiple myeloma, including the newly approved pomalidomide, but this intriguing class of drugs clearly is also of great interest in B-cell cancers. The last several ASH meetings have included a number of presentations suggesting that len alone or with R ("R squared — R^2") has significant activity in CLL and NHL, and at the 2012 conference the good news continued.

Notably, Dr Nathan Fowler presented the final results of **a Phase II trial** of 110 patients with indolent lymphoma treated with the R^2 regimen. High rates of durable responses were observed, including CRs in 42/45 patients with FL who converted to PET negativity, and this encouraging data set and others have spawned a number of studies like the Phase III RELEVANCE trial comparing R^2 to chemotherapy/R, raising the possibility of a future world without chemotherapy for this disease.

Another Phase II CLL study evaluated a strategy now often used in myeloma, namely len maintenance, in this case for 12 months after BR induction. The encouraging median PFS of 24.3 months in 34 patients has led to interest in testing R^2 maintenance, an approach that is also the focus of a current ECOG MCL trial.

3. Other novel treatments: Chimeric antigen receptor (CAR) therapy, anti-PD-1

The spectacular science and clinical challenges of next-generation biologic therapy were on full display in a **paper profiling the use of CART19 cells** targeting the CD19 antigen, which is expressed on the surface of most B-cell cancers. This Star Wars-like treatment involves gene transfer techniques to genetically modify T cells, which in this study was demonstrated to have rapid and potent antitumor activity in chemotherapy-refractory CD19-positive CLL and ALL. The development of a cytokine release syndrome in some cases is a signal for caution in this maybe revolutionary approach to immune-based treatment.

Similarly, while anti-PD-1 has gotten a lot of press across solid tumor oncology, this immunotherapeutic strategy is also under investigation in hematologic cancers. In this regard, an **early paper** reported encouraging results with the combination of R and the anti-PD-1 monoclonal antibody pidilizumab (CT-011) in patients with RR FL.

While ASH was a treasure trove of exciting papers on biologics, more is on the way, as witnessed by a recent **press release** concerning a large Phase III German CLL trial evaluating the glycoengineered, humanized type II CD20 antibody obinutuzumab (O; GA101) that reported an advantage to adding this agent to chlorambucil (CLB), but this is just an appetizer to the main dish — the comparison to R-CLB. R seems to have less activity in CLL than in many lymphomas, and the hope is that O will yield greater benefit.

Next on this ASH series — new data on myelofibrosis, a cancer that finally has effective but complex treatment options, including 2 key follow-up reports of landmark Phase III trials of ruxolitinib.

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 1.75 *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 Celgene Corporation, Genentech BioOncology/ Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva Oncology.

The Btk Inhibitor Ibrutinib (PCI-32765) Alone and in Combination with Rituximab for CLL or SLL

Presentations discussed in this issue

Byrd J et al. **The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib (PCI-32765) promotes high response rate, durable remissions, and is tolerable in treatment naïve (TN) and relapsed or refractory (RR) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) patients including patients with high-risk (HR) disease: New and updated results of 116 patients in a Phase Ib/II study.** *Proc ASH* 2012;**Abstract 189**.

Burger J et al. **The Btk inhibitor ibrutinib (PCI-32765) in combination with rituximab is well tolerated and displays profound activity in high-risk chronic lymphocytic leukemia (CLL) patients.** *Proc ASH* 2012;**Abstract 187**.

Slides from presentations at ASH 2012 and transcribed comments from a recent interview with Bruce D Cheson, MD (1/14/13)

The Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) Promotes High Response Rate, Durable Remissions, and is Tolerable in Treatment-Naïve (TN) and Relapsed or Refractory (RR) Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Patients Including Patients with High-Risk (HR) Disease: New and Updated Results of 116 Patients in a Phase Ib/II Study

Byrd JC et al.

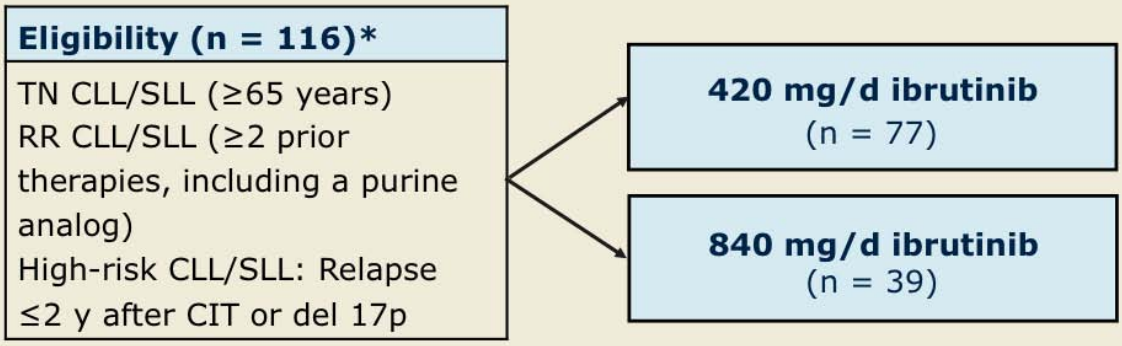
Proc ASH 2012;Abstract 189.

Background

- Although fludarabine-based chemoimmunotherapy (CIT) is effective, it is not well tolerated by elderly patients (pts) and nearly all patients experience relapse after fludarabine-based CIT.
- Ibrutinib is an oral inhibitor of BTK, an essential mediator of B-cell receptor signaling, that promotes apoptosis and inhibits proliferation, migration and adhesion in CLL cells (*Blood* 2012;119:1182).
- Recent Phase I study results with ibrutinib demonstrated high response rates in pts with RR B-cell lymphoma and CLL (*J Clin Oncol* 2013;31:88).
- **Study objective:** To evaluate the efficacy and safety of ibrutinib monotherapy at 2 different doses for patients with TN and RR CLL or SLL.

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

Phase Ib/II Trial Design



* Patients were divided into 5 cohorts between the 2 dosing regimens.

- **Primary endpoint:** Safety
- **Secondary endpoints:** Efficacy, pharmacokinetic/pharmacodynamic (PK/PD) analysis and long-term safety

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

Research To Practice®

Patient Cohorts (Abstract Only)

Cohort	Population with CLL/SLL	Dose	n
1	Relapsed or refractory	420 mg/d	27
2	TN (≥65 years)	420 mg/d	26
3	Relapsed or refractory	840 mg/d	34
4	High-risk	420 mg/d	24
5	TN (≥65 years)	840 mg/d	5*

* Cohort was closed prior to full accrual after comparable activity and safety between doses was observed with patients with RR disease

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

Research To Practice®

Best Response by Cohort (Abstract Only)

Response rate	Cohorts 2 & 5 (n = 31)	Cohorts 1 & 3 (n = 61)	Cohort 4 (n = 24)
ORR	71%	67%	50%
CR	10%	3%	0%
PR	61%	64%	50%
PR with lymphocytosis	10%	20%	29%
Stable disease	13%	5%	8%
Progressive disease	0%	2%	4%
Not evaluable	6%	7%	8%

ORR = overall response rate; CR = complete response; PR = partial response

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

Research To Practice®

Survival Rates (Abstract Only)

Patients with RR or high-risk disease	n = 85
Estimated 22-month progression-free survival (PFS)	76%
Estimated 22-month overall survival (OS)	85%
Patients with TN disease (≥65 years)	**n = 31**
Estimated 22-month PFS	96%
Estimated 22-month OS	96%

- Median PFS and OS have not been reached for any of the 5 cohorts.
- Responses were independent of poor-risk factors, including advanced disease, prior lines of therapy, beta-2 microglobulin or cytogenetics.

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

Research To Practice®

Clinical Observations (Abstract Only)

- Serial evaluation of serum immunoglobulins (Ig) revealed:
  - A significant increase in IgA at 3, 6 and 12 months ($p < 0.005$).
  - No decline in IgG and IgM.
- 56/69 patients with relapsed disease with wild-type IgVH developed treatment-related lymphocytosis.
  - Median time to normalization: 6.2 months
- 11/11 patients with mutated IgVH developed treatment-related lymphocytosis.
  - Median time to normalization: 14.8 months
- Lymphocytosis was normalized at a higher frequency in patients with wild-type versus mutated IgVH (86% vs 55%; $p < 0.04$).

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

Research To Practice®

Select Adverse Events (Abstract Only)

Grade ≤2 Adverse Events (AEs)	n = 116
Diarrhea	54%
Fatigue	29%
Upper respiratory tract infection	29%
Rash	28%
Nausea	26%
Arthralgia	25%

- Treatment discontinuation due to AEs: 6%
- Hematologic AEs ≥Grade 3 were infrequent
- No evidence of cumulative toxicity or long-term safety concerns after a median follow-up of 16 months

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

Research To Practice®

Author Conclusions (Abstract Only)

- Ibrutinib monotherapy is highly active, well tolerated and induces durable remissions in patients with RR and high-risk CLL and in elderly patients with treatment-naïve CLL.
- Based on these results, a Phase III study of ibrutinib in these populations of patients is warranted.

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

Research To Practice®

The Btk Inhibitor Ibrutinib in Combination with Rituximab (iR) is Well Tolerated and Displays Profound Activity in High-Risk Chronic Lymphocytic Leukemia (CLL) Patients

Burger JA et al.

Proc ASH 2012;Abstract 187.

Research To Practice®

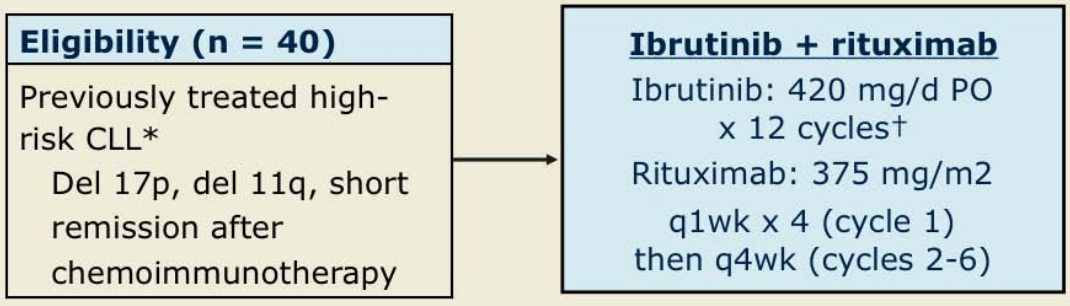
Background

- Currently, there is no standard treatment for patients with high-risk CLL, whose disease has shorter remissions and a poor outcome with conventional CIT.
- Single-agent ibrutinib elicits a good response in patients with high-risk CLL (*Proc ASH* 2011;Abstract 983).
- However, treatment of CLL with single-agent ibrutinib often results in delayed responses or stable disease due to the development of persistent lymphocytosis.
- **Study objective:** To evaluate the activity and tolerability of ibrutinib/rituximab combination therapy for high-risk CLL.

Burger JA et al. *Proc ASH* 2012;Abstract 187.

Research To Practice®

Phase II Trial Design



* Patients with untreated CLL with del 17p or mutant TP53 were eligible.

† Patients with benefit after cycle 12 were allowed to continue receiving single-agent ibrutinib.

Burger JA et al. *Proc ASH* 2012;Abstract 187.

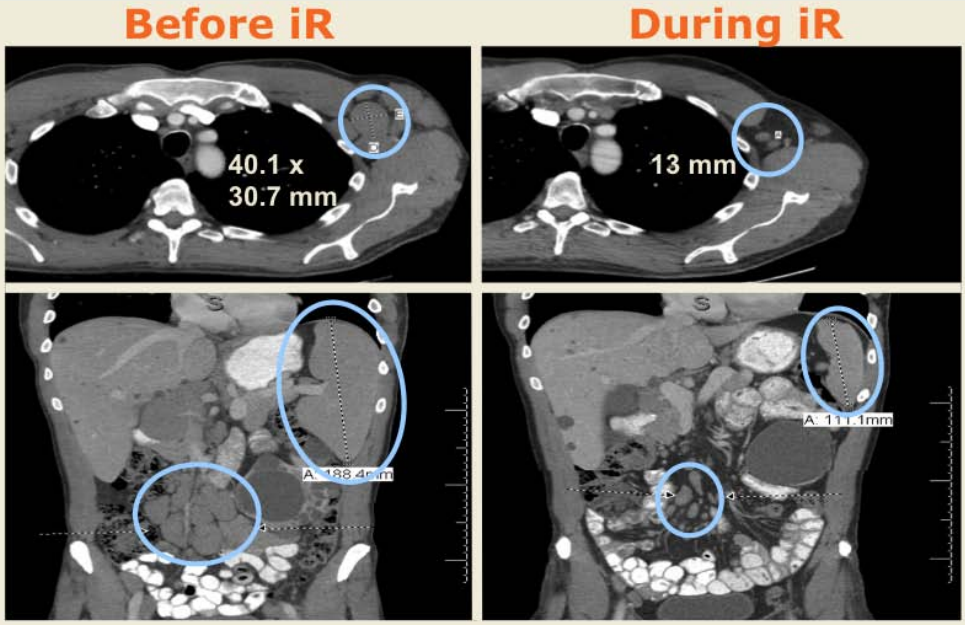
Research To Practice®

Assessment by Computed Tomography (CT) at 3-6 Months (n = 31)

With permission from Burger JA et al. *Proc ASH* 2012;Abstract 187.

Research To Practice®

Radiographic Response to Ibrutinib/ Rituximab Therapy



Axillary lymphadenopathy, abdominal nodes and splenomegaly all regressed during therapy.

With permission from Burger JA et al. *Proc ASH* 2012;Abstract 187.

Research To Practice®

Response Rates at 3-6 Months

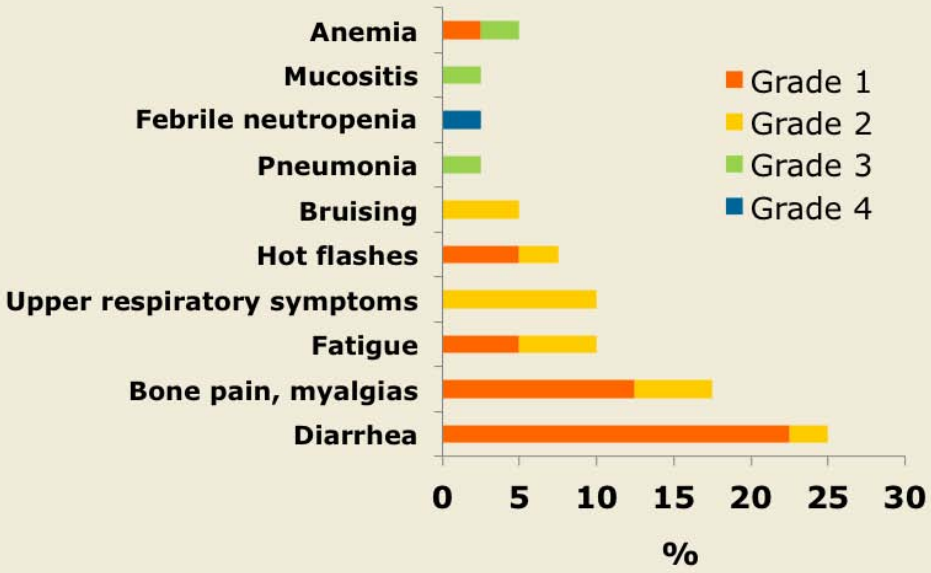
Response	n = 40
Overall response rate	83%
Complete response	3%
Partial response (PR)	80%
PR with persistent lymphocytosis	8%
Stable disease	5%

It was too early for assessments for 2 patients.

Burger JA et al. *Proc ASH* 2012;Abstract 187.

Research To Practice®

Adverse Events



Discontinuation of therapy due to aspergillosis (n = 1), oral ulcers (n = 1)

With permission from Burger JA et al. *Proc ASH* 2012;Abstract 187.

Research To Practice®

Author Conclusions

- The combination of ibrutinib with rituximab demonstrated profound activity in patients with high-risk CLL.
  - ORR: >80%
  - Favorable toxicity profile with no hematologic toxicities observed
- The addition of rituximab to ibrutinib therapy may accelerate response in comparison to single-agent ibrutinib.
- However, the duration of remission in addition to the long-term side effects of combining ibrutinib with rituximab are unknown.
- Ibrutinib alone or in combination with rituximab should be rapidly developed for the treatment of high-risk CLL.

Burger JA et al. *Proc ASH* 2012;Abstract 187.

Research To Practice®

Investigator Commentary: Efficacy and Tolerability of the BTK Inhibitor Ibrutinib (PCI-32765) Alone and in Combination with Rituximab for Patients with CLL

Dr Byrd presented the single-agent ibrutinib data for patients with TN, RR or high-risk CLL and the response rates were phenomenal. Overall response rate (ORR) in the untreated cohort was more than 70% and was 67% in the RR population. ORR for patients at high risk — those with 17p deletion or with an extremely short initial response to treatment — was 50%. Another striking feature of this study was the progression-free survival (PFS) numbers — for patients with TN CLL it was more than 90% and for those with RR disease it was more than 70%. Even for those patients with 17p deletion, PFS was in the 50% to 60% range. We've never seen responses like those in that patient population.

The next logical step was to combine this agent with rituximab. A presentation by Dr Burger reported an early response assessment for this combination in a small number of patients with high-risk CLL. The ORR was 83% with a relatively short follow-up, but they were astounding results nonetheless. You're combining a pill with rituximab, and more than 80% of patients respond and the combination is well tolerated.

Interview with Bruce D Cheson, MD, January 14, 2013