5 Minute JournalClub

POST-ASH Issue 4, 2014

Updated Results of a Phase II Trial of Ibrutinib and Rituximab for High-Risk 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. 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.

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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

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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

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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

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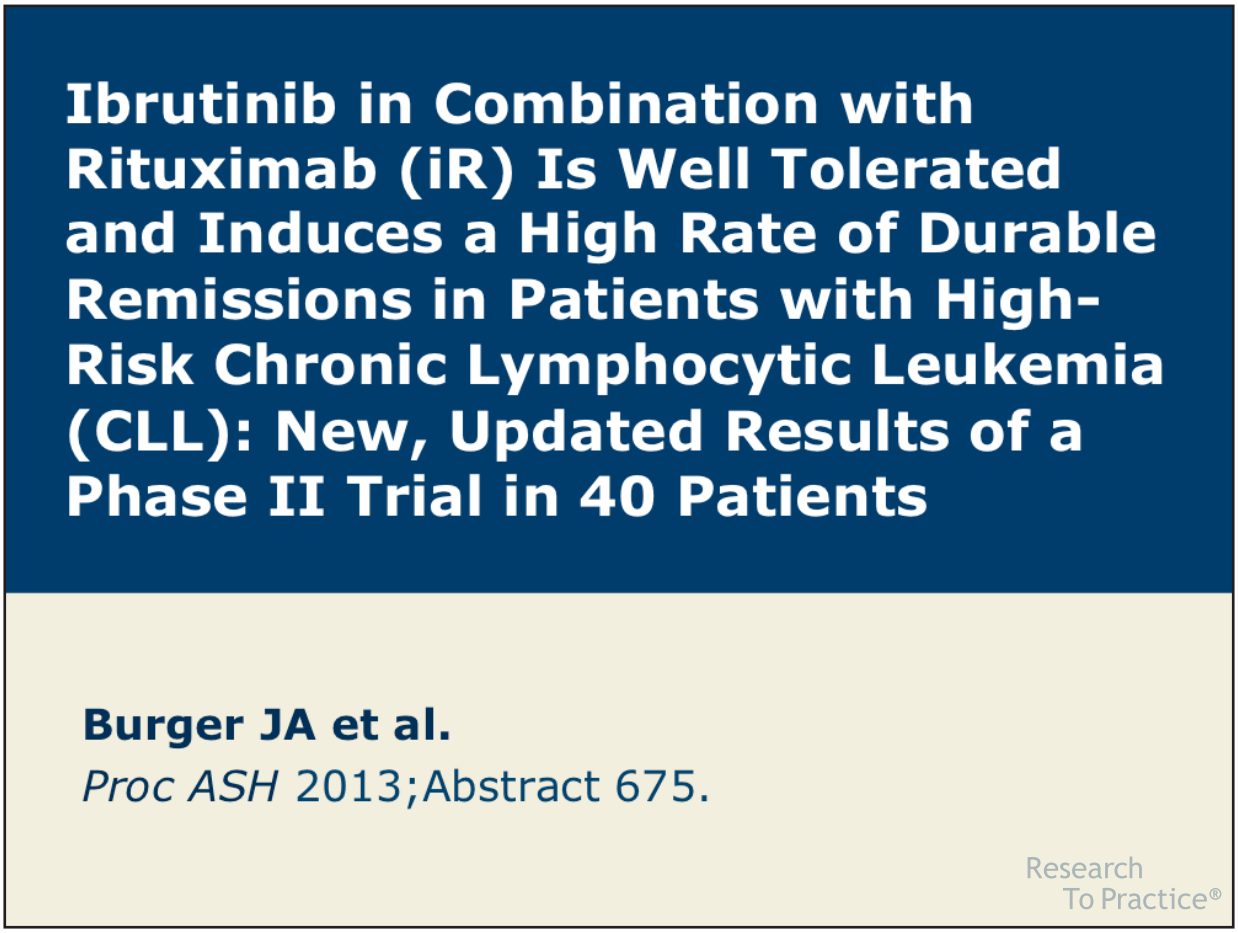
Updated Results of a Phase II Trial of Ibrutinib and Rituximab for High-Risk CLL

Presentation discussed in this issue

Burger JA et al. **Ibrutinib in combination with rituximab (iR) is well tolerated and induces a high rate of durable remissions in patients with high-risk chronic lymphocytic leukemia (CLL): New, updated results of a Phase II trial in 40 patients.** *Proc ASH* 2013;**Abstract 675**.

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



Background

- The Bruton tyrosine kinase inhibitor ibrutinib is a promising new targeted therapy for patients with mature B-cell hematologic cancers, especially chronic lymphocytic leukemia (CLL).
- Ibrutinib monotherapy induces high rates of durable responses in patients with previously treated CLL (*N Engl J Med* 2013;369:32):
  - Overall response rate (ORR) = 71%, with an additional 15% to 20% of patients experiencing partial response with lymphocytosis, which is generally transient (peaks after 1 to 2 months and then continuously declines)
  - Responses are independent of prognostic factors, such as del(17p)
  - At 26 months: Progression-free survival (PFS) = 75%, overall survival (OS) = 83%
- **Study objective:** To assess the activity and tolerability of ibrutinib and rituximab combination therapy (iR) in patients with high-risk CLL.

Burger JA et al. *Proc ASH* 2013;Abstract 675.

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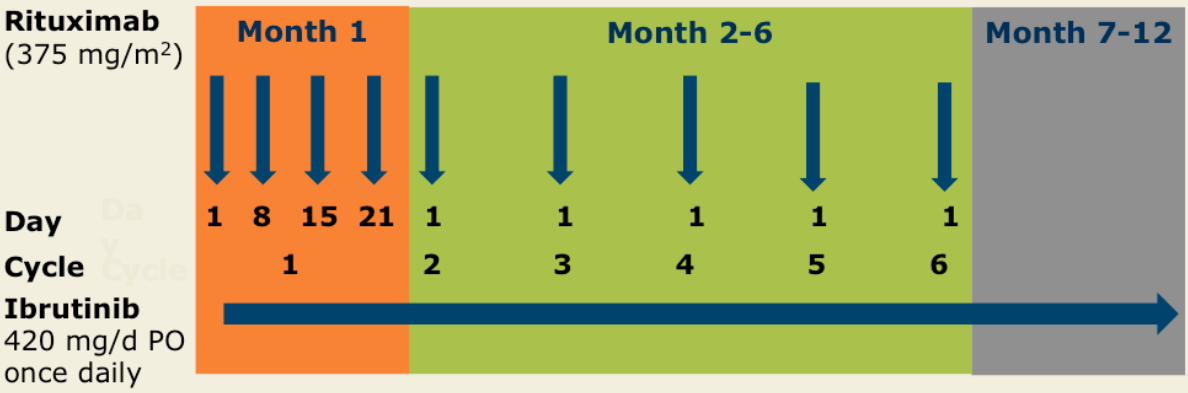
Phase II Trial Design: Dose and Schedule of iR



Patients with benefit after 12 cycles will be allowed to continue on single-agent ibrutinib.

Burger JA et al. *Proc ASH* 2013;Abstract 675.

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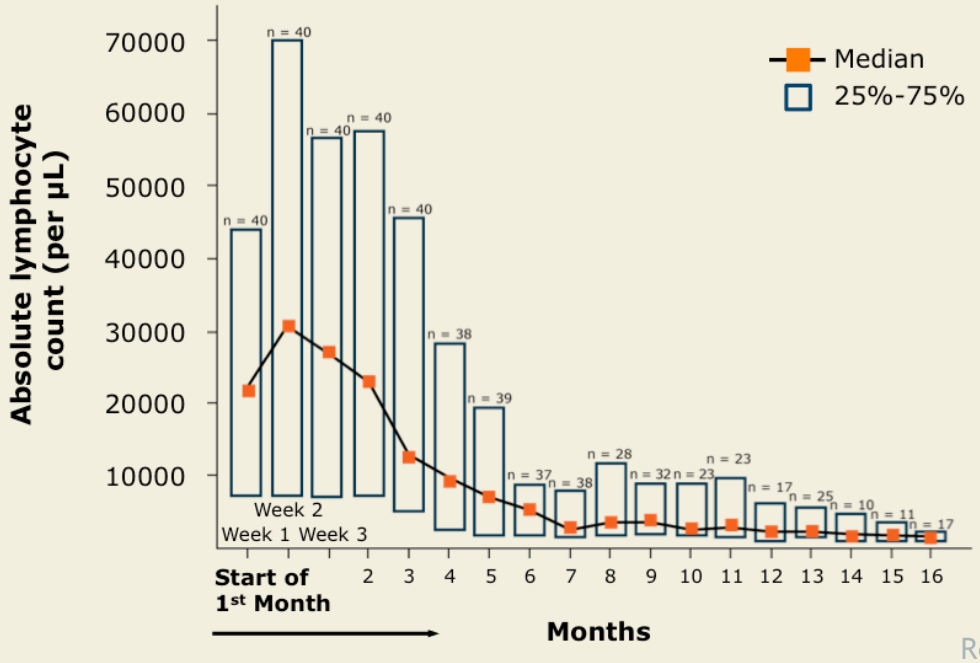
Transient Lymphocytosis on iR Therapy



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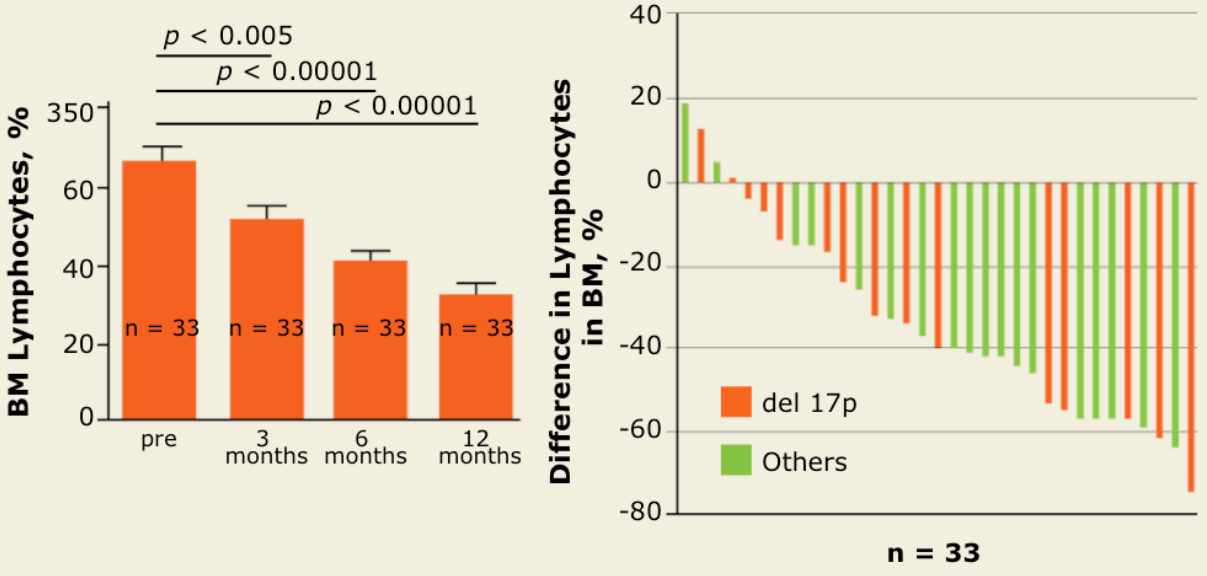
Changes in Bone Marrow (BM) Infiltration During iR Therapy



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Best Response*

n = 40	n (%)
ORR	38 (95%)
Complete response†	4 (10%)
Partial response	34 (85%)
No response	2 (5%)

* At 12 months or best response before study discontinuation

† Minimal residual disease (MRD)-negative: 1 out of 4 patients; MRD level: 0.1%, 0.2%, 0.1%

Burger JA et al. *Proc ASH* 2013;Abstract 675.

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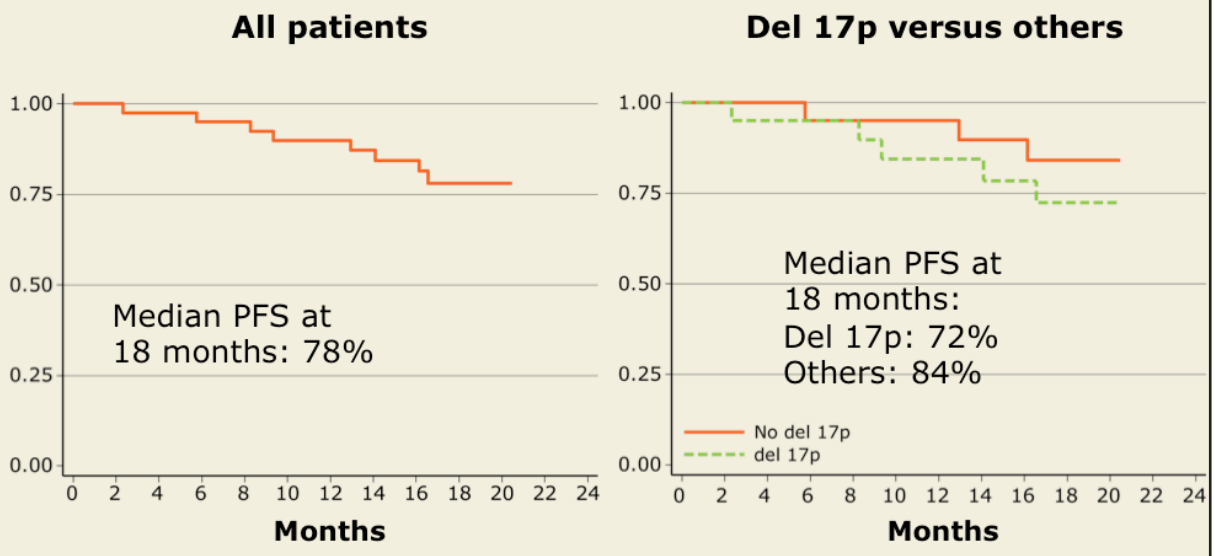
PFS



Median follow-up: 17 months

With permission from Burger JA et al. *Proc ASH* 2013;Abstract 675.

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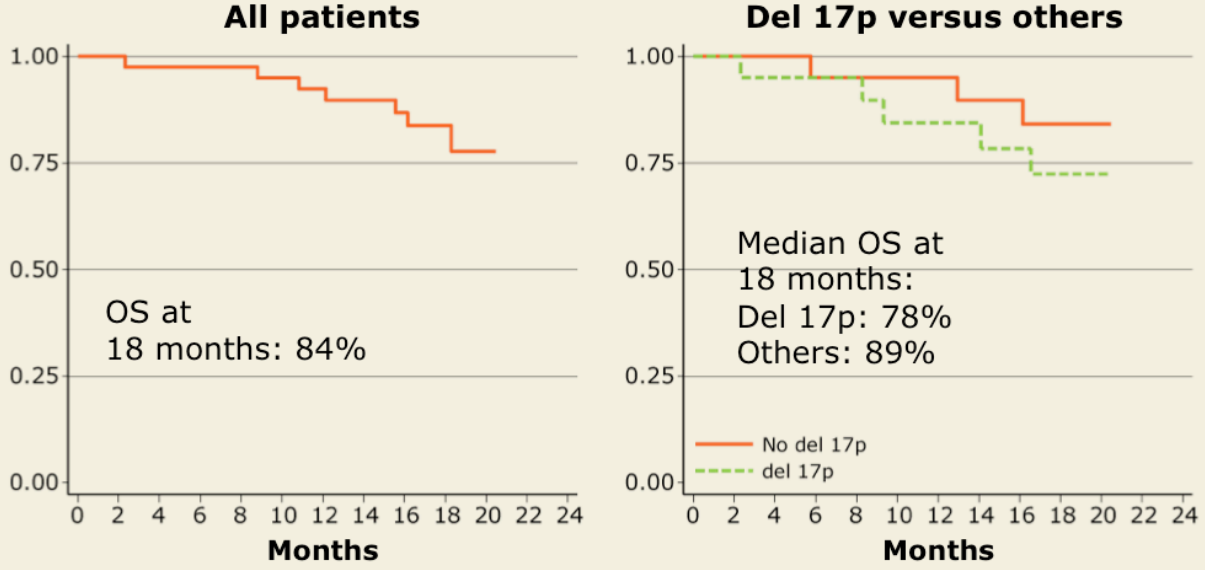
OS



Median follow-up: 17 months

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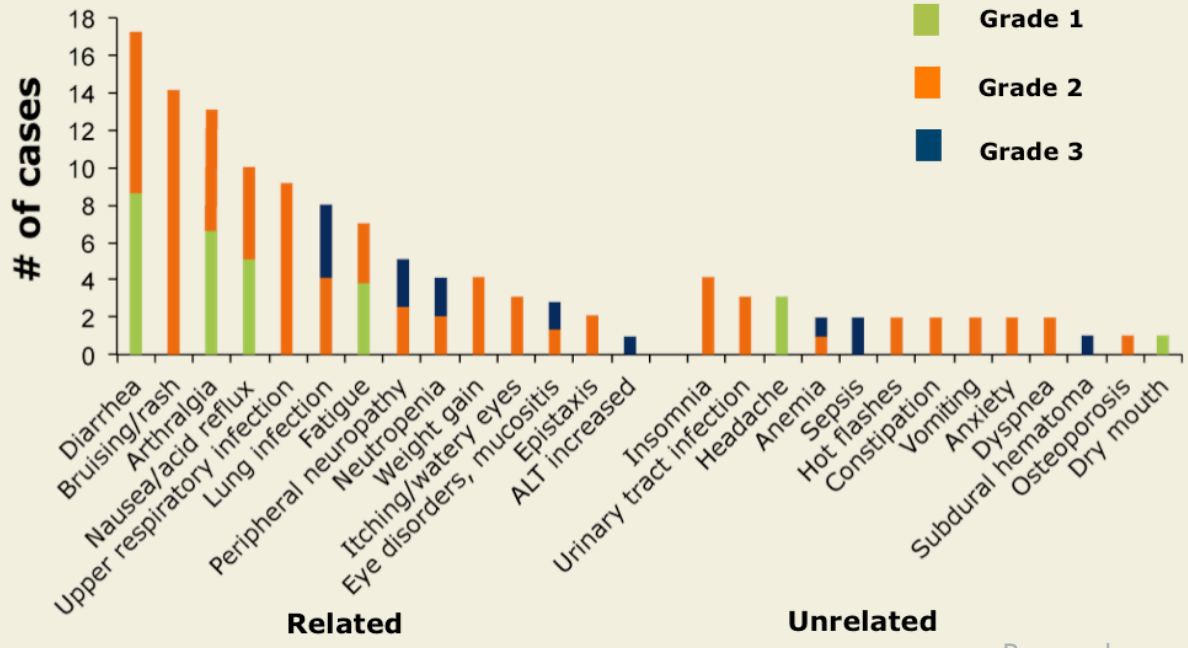
Adverse Events



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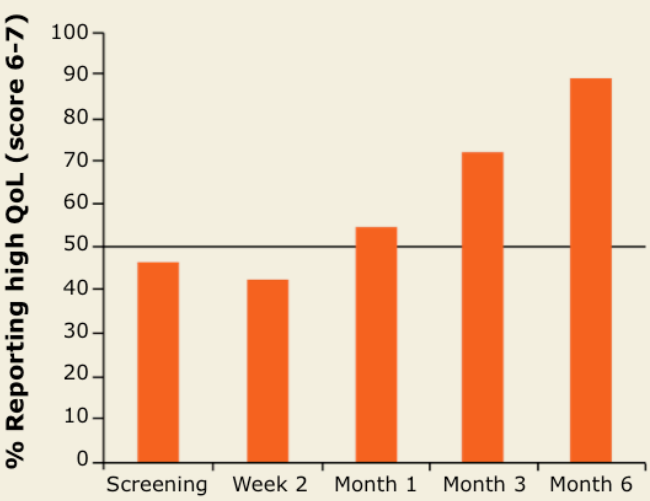
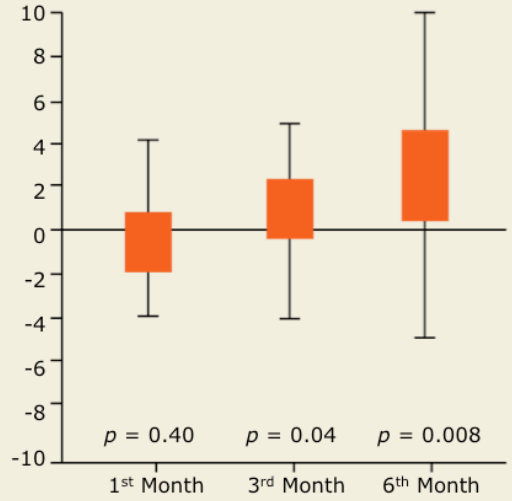
Quality of Life (QoL) and Body Weight Improvement During iR Therapy





Percentage of patients who score highly in the QoL subscales (values 6-7) of the EORTC-QOLv.3 during iR therapy

Baseline Mean KG (SD)	After Cycle 1 (SD)	After Cycle 3 (SD)	After Cycle 6 (SD)
79.15 (18.88), n = 40	78.84 (19.09) n = 40	79.94 (19.01) n = 39	80.99 (18.61) n = 37
	Δ = -0.32 (2.38) p = 0.04	Δ = 0.09 (2.65) p = 0.04	Δ = 1.74 (3.8) p = 0.008

With permission from Burger JA et al. *Proc ASH* 2013;Abstract 675.

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Author Conclusions

- The combination of ibrutinib and rituximab has profound activity in patients with high-risk CLL:
  - ORR >90%, CR = 10%
- The combination has a favorable toxicity profile and improves BM infiltration and function.
- The addition of rituximab accelerates ibrutinib response in CLL.
- iR is well tolerated and associated with improvements in QoL and body weight.
- A randomized Phase II follow-up study of ibrutinib versus iR for patients with relapsed CLL is under way (NCT02007044).

Burger JA et al. *Proc ASH* 2013;Abstract 675.

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Investigator Commentary: Updated Results of a Phase II Trial of iR for Patients with High-Risk CLL

Single-agent ibrutinib is a well-tolerated agent, but its use has been associated with lymphocytosis. The rationale behind this trial was that the addition of a monoclonal antibody should help in getting rid of the lymphocytosis immediately. Forty patients with relapsed/refractory, high-risk CLL received the ibrutinib/rituximab combination. The investigators reported impressive results. The overall response rate in this patient cohort was 95%, and 18-month PFS was 78%. My conclusion from this study is that if you add rituximab to ibrutinib, lymphocytosis resolves much more quickly than if you administer ibrutinib alone.

I believe that the real question is, does that translate to a clinically meaningful advantage for the patient? In other words, is it actually beneficial to get rid of those circulating lymphocytes immediately rather than letting them die off more slowly over the next couple of months, which is what happens with single-agent ibrutinib? We don't know the answer to that yet. It will take randomized trials comparing ibrutinib to iR or ibrutinib/obinutuzumab to answer that question and ascertain whether adding the monoclonal antibody provides a meaningful benefit for patients.

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