



*POST-ASH* Issue 6, 2015

# Phase II PCYC-1111 Trial of Ibrutinib with or without Dexamethasone in Relapsed/Refractory MM

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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 novel agents and salvage therapeutic options for the treatment of relapsed or refractory multiple myeloma (MM) and Waldenström macroglobulinemia (WM), high-risk smoldering MM (SMM) and the front-line management of AL amyloidosis 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

- Evaluate the final efficacy and safety results from the Phase I/II 1703 study of elotuzumab in combination with lenalidomide and dexamethasone for patients with relapsed/refractory MM.
- Appraise recent clinical research findings on the effectiveness of the monoclonal anti-CD38 antibodies SAR650984 and daratumumab in combination with lenalidomide and dexamethasone in relapsed/refractory MM.
- Investigate the efficacy and safety of ibrutinib as a single agent or in combination with dexamethasone in relapsed or relapsed/refractory MM.
- Compare and contrast the benefits and risks of lenalidomide and low-dose dexamethasone with or without carfilzomib for patients with high-risk SMM.
- Analyze the role of front-line cyclophosphamide in combination with bortezomib and dexamethasone (CyBORd) in AL amyloidosis.
- Assess the safety and efficacy of the proteasome inhibitor oprozomib as a single agent in the treatment of WM.

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**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:

Ola Landgren, MD, PhD  
Chief, Myeloma Service  
Memorial Sloan Kettering Cancer Center  
New York, New York

Contracted Research: Celgene Corporation, Onyx Pharmaceuticals, an Amgen subsidiary.

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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: May 2015

Expiration date: May 2016

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

One of my favorite days of the year occurs every April when the American Society of Clinical Oncology (ASCO) releases their iPlanner for the upcoming annual meeting that provides a first glimpse at the titles of all the oral abstracts that will be presented during the conference. This year my review quickly established that in the world of solid tumors there would be many highlights, including the long-awaited MARIANNE report evaluating pertuzumab and T-DM1 in HER2-positive breast cancer and a ton of impressive checkpoint inhibitor papers in lung cancer (squamous and nonsquamous), melanoma and a number of other diseases.



**Sagar Lonial, MD**

In terms of hematologic cancers, ASCO is always good for a few headline grabbers, and in reviewing the papers, my attention was immediately drawn to the first abstract in the multiple myeloma (MM) oral session — the Phase III ELOQUENT-2 trial in relapsed/refractory (RR) disease. The study, one of the most anticipated in MM in many years, randomized patients to lenalidomide (len)/dexamethasone (dex) alone or combined with the novel monoclonal antibody elotuzumab (elo).

This was definitely not the first time I became aware ahead of time that an important new data set was about to be presented, and as usual I was desperately curious to find out the results. About a week later I had my chance when the principal investigator, Dr Sagar Lonial, participated in a symposium we were doing as part of our always rewarding annual visit to the Oncology Nursing Society Congress. However, as usual my hopes were crushed by a strict embargo, and Sagar was a complete stone-wall Buddha sphinx, rebuffing all my attempts to squeeze the information out of him and leaving me totally clueless whether the study proved what earlier smaller trials suggested, namely that a special synergy exists between this antibody, which has no single-agent activity, and len.

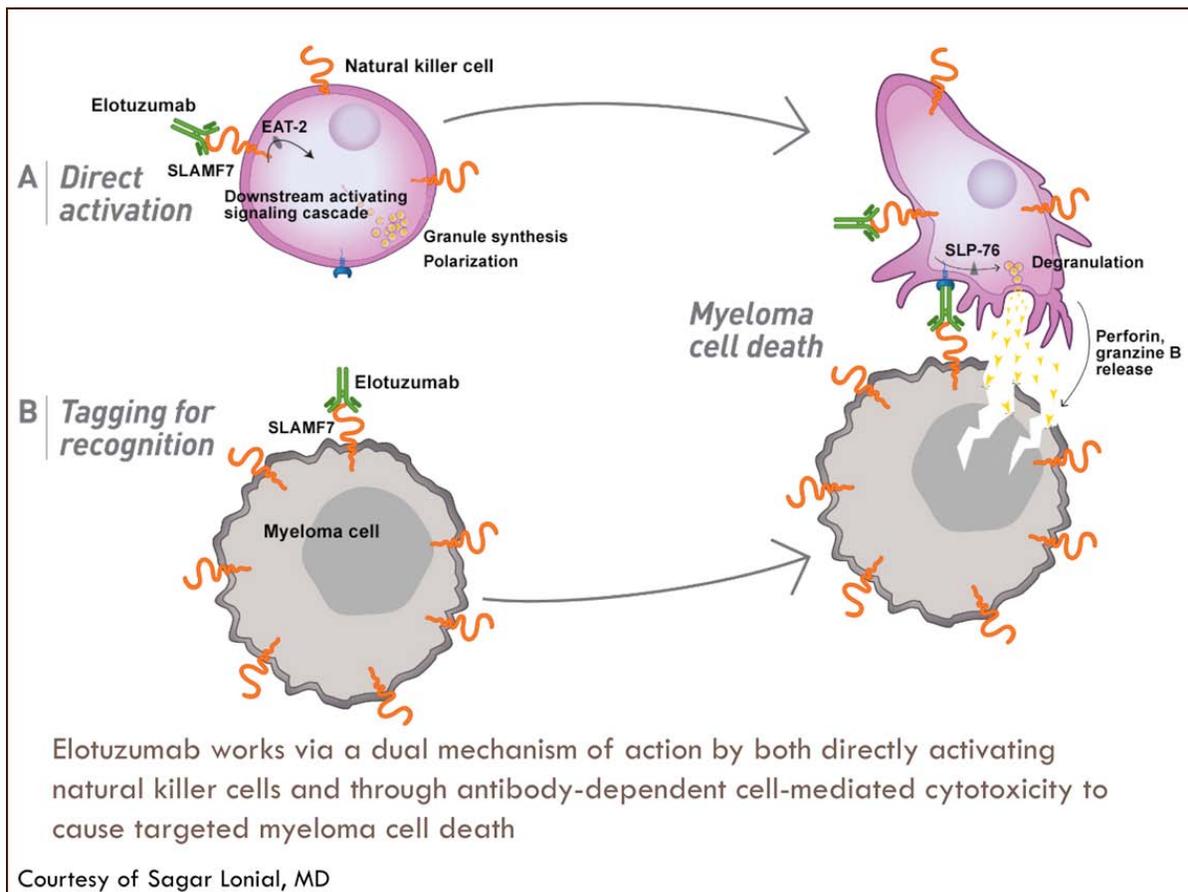
Fast forward to a week ago, when ASCO released online all but the late-breaking abstracts. My first click was to ELOQUENT-2, and to my delight, elo/len/dex resulted in a 30% reduction in the risk of disease progression and also a mortality benefit. While we most definitely need to see the data and hear Sagar and the rest of the myeloma community's take, if first impressions are any indication it could be that finally a cancer of cells that produce antibodies is soon going to have one as part of its treatment.

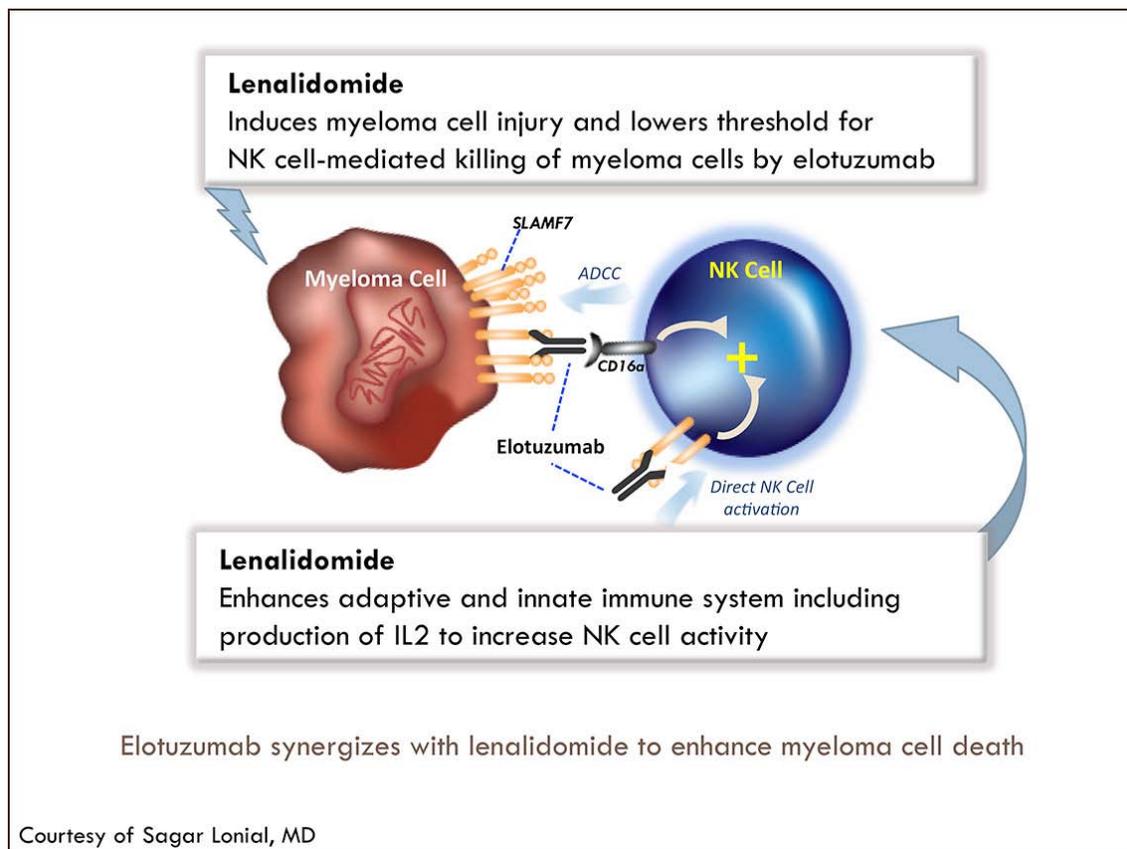
However, until the fun begins in Chicago, there is still much work to be done, and this issue of our American Society of Hematology (ASH) review series highlights a number of new directions in the treatment of MM, including antibodies, and several other related (at least in terms of who manages them) diseases, including Waldenström macroglobulinemia and AL amyloidosis.

## Monoclonal antibodies in MM

### • Elo/len/dex

After years of asking investigators to explain how immunomodulating drugs work (and still not completely understanding the answer), I suspect that elo may be even more of a challenge. Signaling lymphocytic activation molecule F7 (SLAMF7) is a glycoprotein that is highly expressed on MM and natural killer (NK) cells but not on normal tissue. As a monoclonal antibody targeted against SLAMF7, elo is thought to directly activate and engage NK cells and selectively target SLAMF7-expressing MM cells for destruction.





As we learn more about the biologic basis of the apparently important synergy of len and elo, ongoing trials are evaluating this approach clinically. At ASH we saw Paul Richardson's [report of 73 patients](#) with RR MM who were treated with this regimen in the Phase II portion of the 1703 study, revealing similar encouraging outcomes as a prior single-arm study (response rate: 84%) with good tolerability. The bottom line now is that on Tuesday, June 2nd at 9:45 AM in the McCormick Place Convention Center, we will find out just how much it helps patients.

### ● **Anti-CD38 antibodies with len/dex**

While elo may be first with Phase III data, among MM investigators there is perhaps even more excitement about anti-CD38 agents, particularly daratumumab (dara) and the as yet nameless SAR650984 (sar). For quite some time now on our CME programs we have been hearing about the single-agent activity of these compounds, and I can recall a number of cases with impressive responses after disease progression on multiple therapies. However, the future of MM treatment seems to be combinations, which are firmly entrenched in the induction setting and gaining traction in RR disease. Thus it is no surprise to see strategies like [the 2 featured here](#) of combining these antibodies with len/dex and producing very good outcomes (77% very good partial response or greater with dara/len/dex; 64.5% overall response rate with sar/len/dex). Many investigators, including Dr Lonial, believe that depth of response is critical in MM, and the hope has been that bringing in new classes of effective agents might push the disease into a more prolonged remission, also raising the possibility of cure as a treatment goal. Much more to come.

## **Ibrutinib in MM**

Ibrutinib has been a revelation in terms of efficacy and activity across many variants of non-Hodgkin lymphoma, and when laboratory evidence emerged regarding the activation of Bruton tyrosine kinase in MM cells, there was optimism that this drug might play an important role in the management of this disease. Unfortunately, at ASH we saw data from [a Phase II trial](#) evaluating ibrutinib as a single agent or in combination with dex for patients with RR MM that demonstrated modest, somewhat underwhelming activity (clinical benefit rate of 8% with single-agent ibrutinib and 25% with the combination of ibrutinib/dex). Although further research is ongoing, few are optimistic that ibrutinib in MM will be anything close to what it is in chronic lymphocytic leukemia and mantle-cell lymphoma.

## **High-risk smoldering MM (SMM)**

Although the standard therapy for these patients continues to be observation, a variety of predictive factors identify a subgroup with at least a 75% risk of disease progression at 5 years. As such, there continues to be significant interest in whether early intervention could help improve outcomes for these patients. In this regard, in San Francisco we saw more follow-up from the [landmark Spanish Phase III QUIREDEX trial](#) that had previously demonstrated an important benefit with the use of len/low-dose dex. With a median follow-up of 64 months, these findings continue to be positive, revealing that progression to symptomatic disease occurred in 25% of patients who received treatment versus 85% in the control group (overall survival rate at 7 years: 94% versus 64% with a hazard ratio of 4.6 and  $p = 0.001$ ).

The NCI group formerly led by Ola Landgren, MD, PhD decided to take things even further and evaluate a triplet regimen, in this case carfilzomib/len/dex, followed by len maintenance in patients with high-risk SMM. Among the 12 patients who received treatment in this manner, 10 became MRD-negative after 8 cycles as determined by next-generation sequencing, which, by way of indirect comparison, appears to be an even greater benefit than the approach taken by the Spanish.

Importantly, a number of ongoing studies are pursuing these encouraging leads, including a major ECOG trial chaired by Dr Lonial in an attempt to confirm the Spanish len/dex data, and it could very well be that one day soon treating high-risk SMM will become part of practice.

## **Cyclophosphamide/bortezomib/dex (CyBorD) in AL amyloidosis (ALA)**

Based on the results from a number of smaller trials, CyBorD has become one of the most commonly used up-front regimens for the treatment of this disease. To further confirm the benefits of this approach, 2 major ALA centers in London, England and Pavia, Italy prospectively collected findings from 230 cases of patients with newly diagnosed disease who received this regimen. The result is the [largest data set ever reported](#) with up-front CyBorD in the disease, from which a number of important observations can be made. Notably, of 30 patients with Stage I ALA (no cardiac

involvement), 80% responded (56% complete response/very good partial response) and there were no deaths with a median of 25 months of follow-up. Median survival of all patients was 72 months.

However, it appears that cardiac stage was the main determinant of survival, and patients with advanced heart disease (defined as those with N-terminal pronatriuretic peptide type B >8,500 ng/L) had poor outcomes, although 37% did achieve a response and seemed to fare better overall. The key takeaway from this data set is that due to the high clonal response and excellent outcome in early-stage ALA, CyBorD remains a preferred induction option and further research is needed to determine whether autologous stem cell transplant should be initiated as part of up-front treatment.

### **Novel agents in Waldenström macroglobulinemia (WM)**

On January 29, 2015, ibrutinib became the first ever agent approved by the FDA for the management of WM. This significant milestone, along with emerging data indicating the activity of a number of other established and novel therapeutics, has breathed new life and interest into the treatment of this rare disease. At ASH we saw several examples of work attempting to move the field forward, including a Phase I/II trial evaluating [single-agent len](#) in 17 patients with RR WM. Thirty-six percent of these individuals responded to therapy, and with a median follow-up of 36 months, 35% of patients had a progression-free survival greater than 24 months.

Similarly, we also saw data from a Phase Ib/II trial evaluating the oral proteasome inhibitor oprozomib, which, like its intravenous cousin carfilzomib, appears to have significant efficacy in this disease. Notably, responses were observed in 5 of 7 patients refractory to bortezomib, and treatment was reasonably well tolerated, although some of the gastrointestinal toxicity that has plagued this agent was observed. To potentially eliminate this troubling side effect there is great interest in evaluating an extended-release formulation of the agent in both MM and WM.

Next, on the final issue of our ASH series, we check out papers on non-Hodgkin lymphoma, including the evaluation of anti-CD20 maintenance treatment in mantle-cell lymphoma.

Neil Love, MD

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Miami, Florida

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# Phase II PCYC-1111 Trial of Ibrutinib with or without Dexamethasone in Relapsed/Refractory MM

Presentation discussed in this issue

Vij R et al. **Ibrutinib, single agent or in combination with dexamethasone, in patients with relapsed or relapsed/refractory multiple myeloma (MM): Preliminary phase 2 results.** *Proc ASH 2014*; **Abstract 31**.

Slides from a presentation at ASH 2014 and transcribed comments from a recent interview with Ola Landgren, MD, PhD (2/9/15)

## Ibrutinib, Single Agent or in Combination with Dexamethasone, in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma (MM): Preliminary Phase 2 Results

**Vij R et al.**

*Proc ASH 2014*; Abstract 31.

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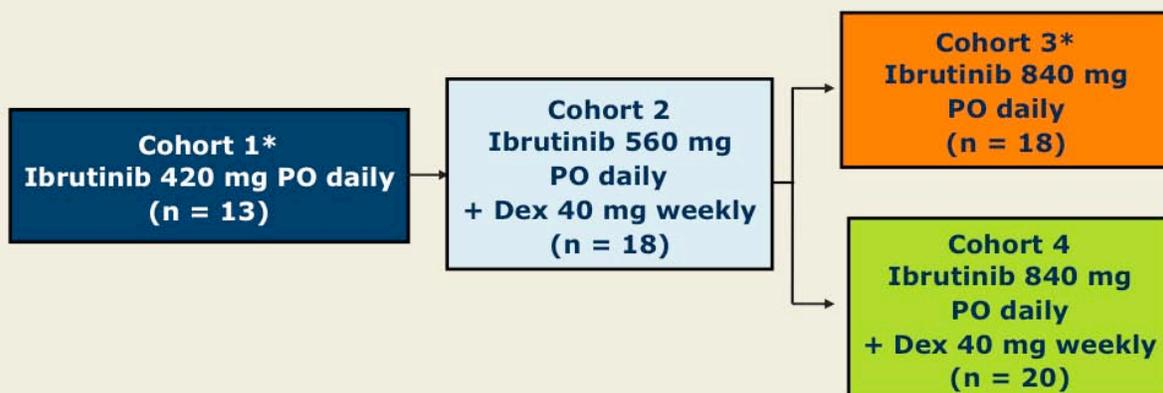
# Background

- Ibrutinib is a first-in-class, once-daily, oral, covalent inhibitor of Bruton tyrosine kinase (BTK), an essential enzyme in the B-cell receptor signaling pathway.
- Preclinical studies show that BTK inhibition with ibrutinib led to direct inhibition of both osteoclast bone resorption and the release of osteoclast-derived tumor growth factors (*Blood* 2012;120:1877).
- Robust BTK expression has been shown in the majority of MM plasma cells (*Am J Hematol* 2013;88:463).
- Taken together, these data suggest that ibrutinib may have a role in the treatment of MM.
- **Study objective:** To investigate the efficacy and safety of ibrutinib as a single agent or in combination with dexamethasone (Dex) in relapsed or relapsed/refractory (R/R) MM.

Vij R et al. *Proc ASH* 2014;Abstract 31.

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## Phase II PCYC-1111 Trial Design



\* For cohorts 1 and 3, the addition of Dex at 40 mg q1wk was permitted at disease progression per investigator discretion.

- **Primary endpoint:** Clinical benefit rate (CBR) defined as minimal response (MR) or better.
- **Secondary endpoints** include duration of clinical benefit, objective response rate, duration of objective response, safety and pharmacokinetic analyses.

Vij R et al. *Proc ASH* 2014;Abstract 31.

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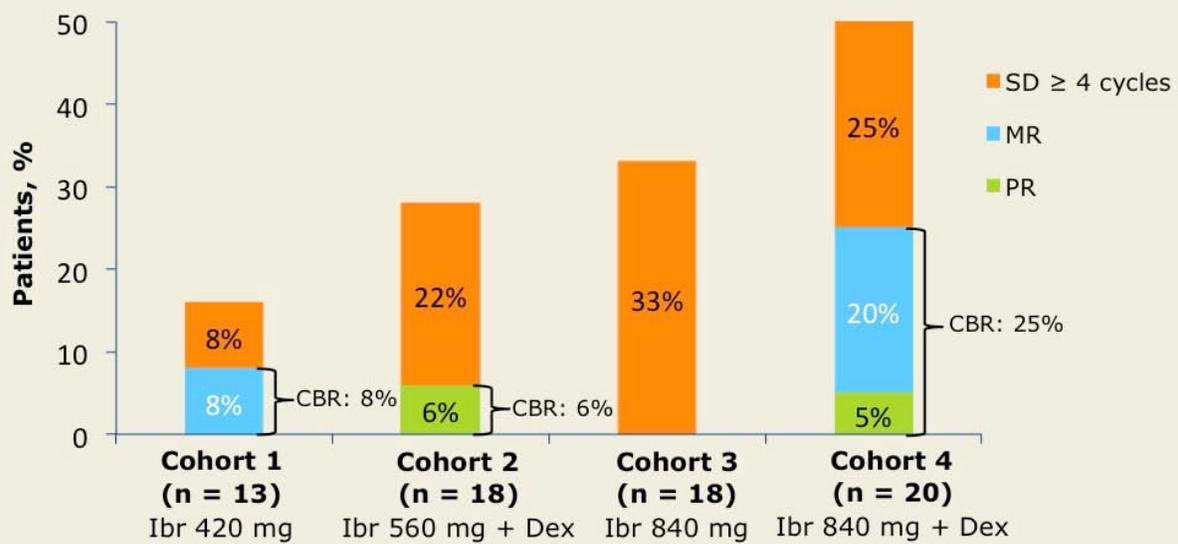
## Key Eligibility Criteria

- Measurable symptomatic relapsed or R/R MM
  - Refractory MM is defined as nonresponsive disease with failure to achieve MR while on treatment, or progressive disease within 60 days of last treatment
- Two or more previous lines of therapy
  - Including an immunomodulatory agent
- ECOG performance status  $\leq 1$
- No inadequate bone marrow function
- No creatinine level  $>2.5$  mg/dL
- No currently active clinically significant cardiovascular disease
- No Grade  $\geq 2$  peripheral neuropathy

Vij R et al. *Proc ASH 2014*;Abstract 31.

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## Overall Response

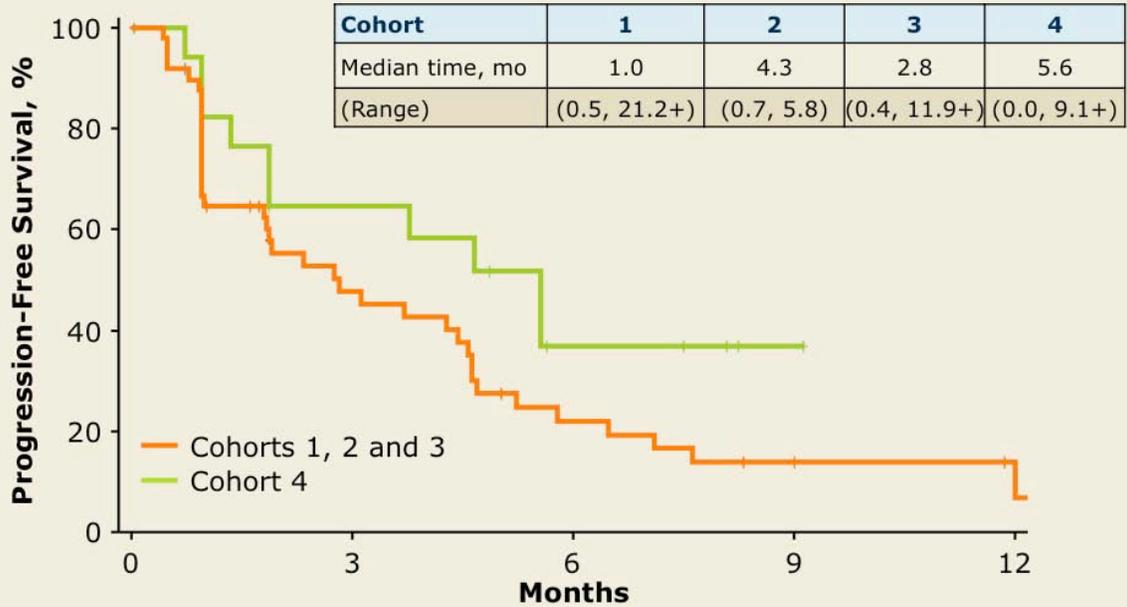


- Rate of disease stabilization or better increased with dose
- CBR rate was 25% for those treated in cohort 4

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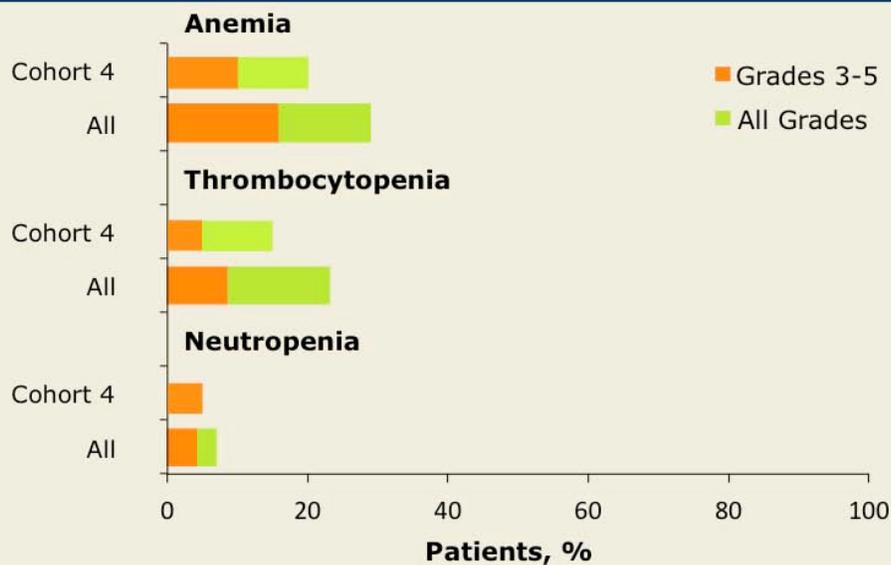
# Progression-Free Survival



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# Hematologic Adverse Events

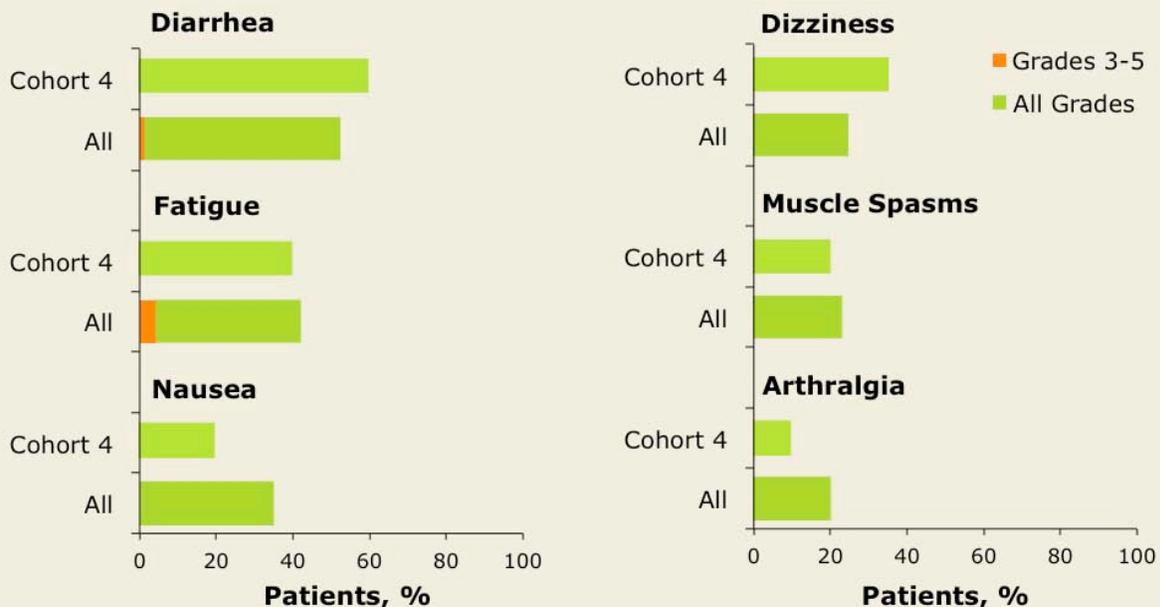


- Grade  $\geq 3$  febrile neutropenia occurred in 2.9% of patients
- 1 patient discontinued treatment due to hematologic adverse events

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# Nonhematologic Adverse Events Occurring in >20% of Patients



- 6 patients discontinued therapy due to nonhematologic adverse events
- With permission from Vij R et al. *Proc ASH 2014*;Abstract 31.

## Author Conclusions

- The safety profile of ibrutinib was tolerable, with similar adverse event rates across dosing cohorts and consistent with those reported in other histologies.
- Ibrutinib with or without weekly Dex demonstrated activity in heavily pretreated relapsed or R/R MM.
- The highest activity was observed in patients in cohort 4:
  - CBR = 25%
  - Sustained stable disease was observed in an additional 25% of patients (data not shown)
  - Median PFS = 5.6 months
- The enrollment of 23 additional patients to cohort 4 is complete, and evaluation of these patients is ongoing.

# Future Directions

- Further study of ibrutinib in combination with other backbone agents is warranted:
  - A Phase Ib/II trial of ibrutinib and carfilzomib is ongoing and has completed enrollment of the dose-escalation phase (NCT01962792)
- Exploratory analysis of ibrutinib in patients with MM will include the determination of:
  - Ibrutinib exposure in comparison to other B-cell cancer types
  - The impact of Dex on ibrutinib exposure
  - The evaluation of potential predictive/prognostic biomarkers, such as markers of bone metabolism, microenvironmental cytokines and chemokines and hematopoietic markers

Vij R et al. *Proc ASH* 2014;Abstract 31.

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## **Investigator Commentary: Efficacy and Safety Results from the Phase II PCYC-1111 Trial for Patients with Relapsed or R/R MM**

These preliminary results from a study of ibrutinib as a single agent or in combination with Dex for patients with relapsed or R/R MM are not impressive. In lymphoma, B-cell receptor signaling is active, and this pathway is one of the drivers of many lymphomas. That is the setting in which ibrutinib is known to be effective. In our laboratory, studies in MM have shown that B-cell receptor signaling is not active in the vast majority of patients. With this knowledge, I was not surprised when I saw these results from the PCYC-1111 trial.

The investigators reported modest responses, with some patients achieving stable disease and some minimal responses, which is the lowest degree of response used for clinical trials. Though disappointing, these results align with what we've observed in our laboratory. Sometimes results obtained in the laboratory are inconsistent with those from clinical trials because drugs may possess additional mechanisms to those already known. I would not have been surprised if ibrutinib proved to be effective in the absence of laboratory evidence. Therefore, these results are important and the study was definitely worth doing.

***Interview with Ola Landgren, MD, PhD, February 9, 2015***

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