5 Minute JournalClub

Hematologic Oncology
Issue 1, 2013

Phase I Study of Weekly MLN9708 in Relapsed/Refractory Multiple Myeloma

For more visit ResearchToPractice.com/5MJCHEM2013

Research To Practice®

CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Clinical Oncology (ASCO) and European Hematology Association (EHA) annual meetings, 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 are aware of crucial practice-altering findings. Unlike ASCO, EHA does not offer access to any of the poster or plenary presentations from the annual meeting via the Internet. This creates an almost insurmountable obstacle for clinicians in community practice because not only are they confronted almost overnight with thousands of new presentations and data sets, 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 in multiple myeloma from the latest ASCO and EHA meetings, including expert perspectives on how these new evidence-based concepts may 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 data on therapeutic advances and potentially practice-changing clinical data in multiple myeloma, and consider this information in clinical practice.
- Evaluate the preliminary safety profiles and response outcomes observed in studies of next-generation proteasome inhibitors, immunomodulatory agents and novel antibodies alone or in combination with approved systemic treatments for patients with relapsed/refractory multiple myeloma.
- Assess the benefits and risks of carfilzomib in combination with an alkylating or immunomodulatory agent for patients with newly diagnosed multiple myeloma.
- Determine the effectiveness and tolerability of pomalidomide in combination with low-dose dexamethasone for patients with relapsed or refractory multiple myeloma and adverse cytogenetics or renal impairment.

ACCREDITATION STATEMENT

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

CREDIT DESIGNATION STATEMENT

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

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCHEM2013/1/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:

Andrzej J Jakubowiak, MD, PhD
Professor of Medicine
Director, Myeloma Program
The University of Chicago
Chicago, Illinois

Advisory Committee: Bristol-Myers Squibb Company, Celgene Corporation, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc; Speakers Bureau: Celgene Corporation.

Antonio Palumbo, MD
Chief, Myeloma Unit
Division of Hematology
University of Torino
Torino, Italy

Consulting Agreements: Bristol-Myers Squibb Company, Celgene Corporation, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Algeta US, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Exelixis 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, Novocure, 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 Genentech BioOncology/Biogen Idec, Onyx Pharmaceuticals Inc 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: September 2013
Expiration date: September 2014

5 MinuteJournalClub

Hematologic Oncology
Issue 1, 2013

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

Antonio Palumbo, MD

The revolution in treatment of multiple myeloma (MM) that occurred over the better part of the last decade is evident in the waiting room of every medical oncologist. Thanks to regimens that include immunomodulatory agents (IMiDs) — particularly lenalidomide (len) — and proteasome inhibitors, specifically bortezomib (bz), along with the widespread utilization of bisphosphonates, it is no longer uncommon to see patients on active treatment for 10 years or more. Of course much is still to be done with this challenging disease, and I met with a leader in the field, Dr Antonio Palumbo, for his take on where we are today and where we might be heading.

For some time Dr Palumbo has been a vocal proponent, along with many other MM investigators, of using the most effective therapies as early as possible in the disease course — often for prolonged durations. Based on his research and that of many others, for younger patients his standard is triple-agent induction followed by high-dose chemotherapy and autologous stem cell transplant and then long-term maintenance treatment. On the flip side, Dr Palumbo has taken a leadership role in the use of preemptive dose reductions for the elderly, allowing for longer-term therapy as opposed to what he calls "short flashes of treatment."

From this clinical framework, Dr Palumbo commented on several new data sets from the ASCO and the European Hematology Association (EHA) annual meetings, attempting to better define the role of the 2 most recently approved agents for MM — carfilzomib

(cz) and pomalidomide (pom) — and several other promising candidates in the later stages of development.

1. Cz triplets

At ASCO this year we saw more on CRd (cz/len/low-dose dexamethasone [lddex]), a cousin of RVD (len/bz/dex), currently one of the most commonly used IMiD/proteasome inhibitor induction regimens.

The final report from the Phase Ib/II trial in relapsed/refractory disease led by Dr Michael Wang that started it all in 2008 demonstrated excellent tolerability with CRd — particularly a lack of significant peripheral neuropathy — and impressive efficacy in patients with extensive prior treatment.

These findings inspired Dr Andrzej Jakubowiak and colleagues to launch an up-front trial that was again reported at ASCO. The antitumor activity in this study is interesting because the depth of response increased with more treatment, and by a median of 22 cycles 87% of patients had achieved a VGPR or better. In keeping with his approach of maximizing the depth of response as early in the disease course as possible, Dr Palumbo is hopeful that accumulating data on CRd and other cz-based up-front regimens will result in an important step forward in induction treatment.

In that context, Dr Palumbo presented at EHA the initial results from a **Phase II up-front trial** evaluating the CCd regimen (cz/cyclophosphamide [cy]/lddex), which resembles another major induction triplet in current practice, CyBorD (cy, bz and dex). CCd was not only well tolerated, but the efficacy seemed equivalent if not superior to that of the bz-based approach.

Similarly, at ASCO and then again at EHA we were treated to **data on CMP** (cz/melphalan/prednisone) as up-front therapy for elderly patients. Again there was significant activity and good tolerability, and while Dr Palumbo believes that both alkylating agent combinations with cz are effective, in his view cyclophosphamide-based regimens are the way forward because of better tolerability.

With the rapid emergence of impressive up-front data with cz regimens, it will be interesting to see whether regulatory agencies, investigators and payers will require direct head-to-head trials against bz-based treatments to see a change in practice. In this regard, the NCCN now lists **CRd as a category 2A up-front option**.

2. Pom/lddex

In December 2012 at ASH Dr Meletios Dimopoulos presented initial findings from the Phase III MM-003 trial documenting an overall survival benefit with the use of pom/

lddex for patients with relapsed/refractory MM. At ASCO and EHA **the results were updated**, and **subset data from this seminal effort** provided evidence of safety and efficacy in patients with moderate renal impairment and modest activity in patients with adverse cytogenetic profiles. In commenting on these studies, Dr Palumbo stated his belief that this regimen provides useful clinical responses in 30% to 50% of patients with disease progressing on len. He also predicted greater long-term benefit if pom/lddex were used earlier in the disease course, ideally soon after progression on another IMiD.

3. Monoclonal antibodies (mAbs)

The recent emergence of 2 distinct compounds with preliminary activity in MM may soon make this disease fertile ground for the regular use of mAbs. The first agent is elotuzumab, which targets the CS1 antigen, and at ASCO and then again at EHA we got more information from Dr Sagar Lonial's **Phase II trial** combining this drug with len and lddex. While this mAb has no single-agent activity, the combination resulted in an eye-popping median PFS of 25.8 months, and one wonders whether we are looking at the myeloma version of "R squared" in lymphoma (len/rituximab). However, Dr Palumbo cautions us to take a conservative view and hold our excitement until Phase III data are available.

Daratumumab, another FDA breakthrough designation recipient, is an anti-CD38 antibody that has shown significant single-agent activity, including an encouraging 31% clinical response rate in a single-arm **Phase I/II dose-escalation study** presented at ASCO and updated at EHA. In Dr Palumbo's eyes CD38 may be as important in MM as CD20 is in lymphoma, and while he won't speculate as to whether the efficacy of this agent will even come close to what we have seen with rituximab in lymphoma, he is enthusiastic about this potential and recently began entering patients on trials of this agent in his own clinic.

4. Oral proteasome inhibitors

The promise of all-oral combination regimens has many excited about MLN9708 (ixazomib), which has a similar structure to bz but lacks the inconvenience of subcutaneous or IV administration. At ASCO Dr Shaji Kumar presented more from an **expanded Phase I study** of ixazomib demonstrating similar efficacy to what has been observed with bz but with improved tolerability. In that regard, Dr Palumbo is particularly interested in seeing this and other oral agents studied in elderly patients for whom the ease of drug delivery might allow more prolonged treatment and greater disease control.

Over the next few years, we shall see if the next generation of new agents and strategies typified by these EHA and ASCO papers bump ahead outcomes similarly to the initial introduction of IMiDs and proteasome inhibitors, but MM investigators including Dr Palumbo seem determined to push the disease at the least into CML-like control and maybe even cure. Next on this series we consider a number of summer papers on CLL, and one data set in particular that may signal a major shift in choice of anti-CD20 antibody in this disease.

Neil Love, MD
Research To Practice
Miami, Florida

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

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

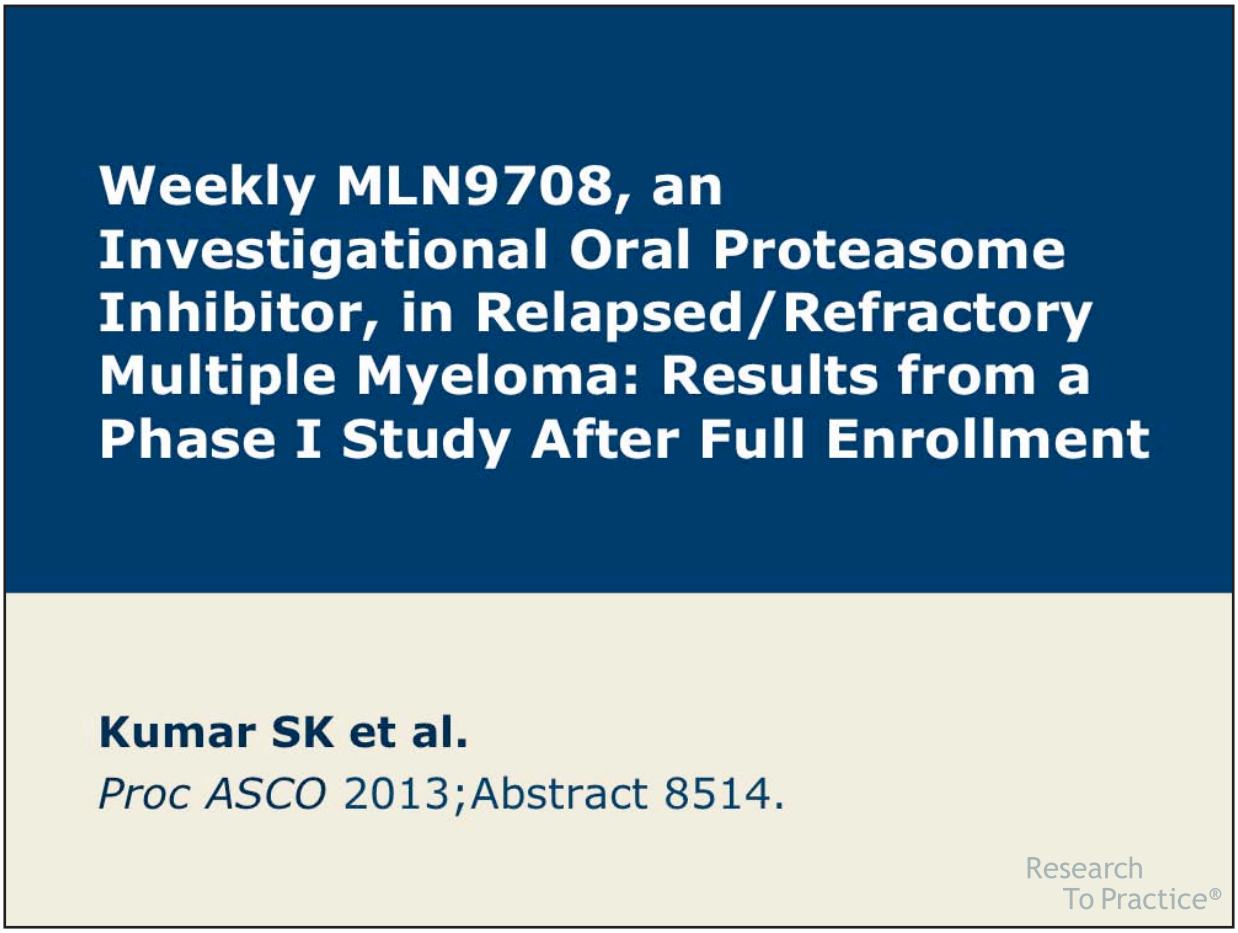
This activity is supported by educational grants from Genentech BioOncology/Biogen Idec, Onyx Pharmaceuticals Inc and Spectrum Pharmaceuticals Inc.

Phase I Study of Weekly MLN9708 in Relapsed/Refractory Multiple Myeloma

Presentation discussed in this issue

Kumar SK et al. **Weekly MLN9708, an investigational oral proteasome inhibitor, in relapsed/refractory multiple myeloma: Results from a Phase I study after full enrollment.** *Proc ASCO* 2013;**Abstract 8514**.

Slides from a presentation at ASCO 2013 and transcribed comments from a recent interview with Antonio Palumbo, MD (8/20/13)



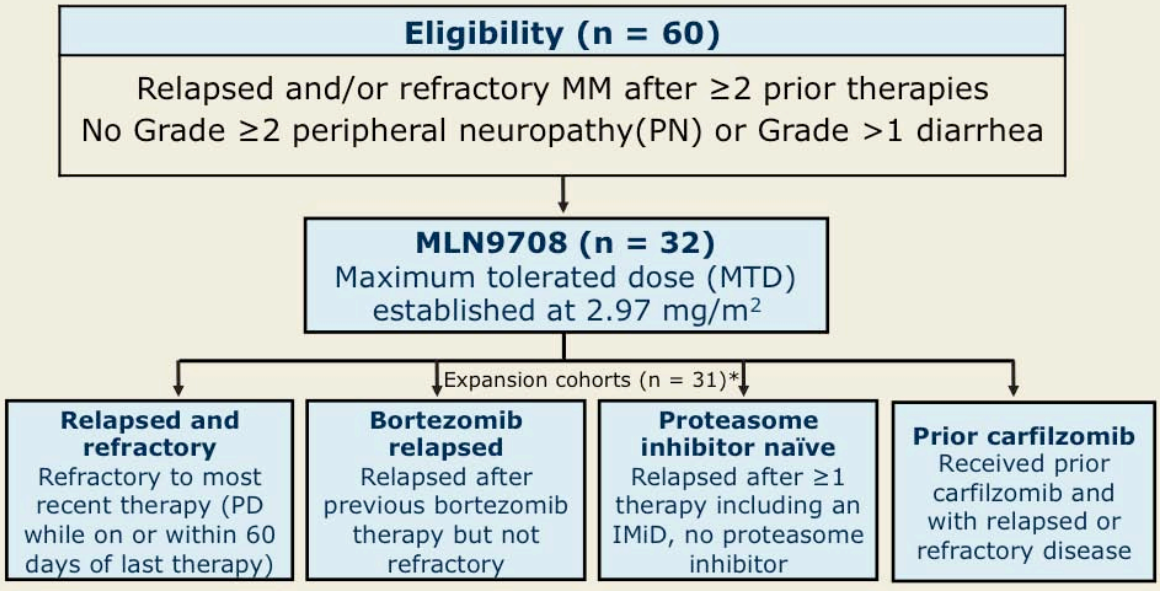
Background

- Proteasome inhibition is one of the most effective antimyeloma strategies, as shown by the efficacy of bortezomib (*N Engl J Med* 2005;352:2487-98).
- MLN9708 (ixazomib) is a potent, investigational, orally bioavailable, reversible inhibitor of the 20S proteasome.
- MLN9708 is the first oral proteasome inhibitor to enter clinical investigation in multiple myeloma (MM).
- **Study objectives:** To determine the maximum tolerated dose, safety, activity and pharmacokinetics of weekly MLN9708 treatment for patients with relapsed and/or refractory MM.

Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

Research To Practice®

Phase I Trial Design



* Includes 3 patients from MTD dose-escalation cohort

Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

Research To Practice®

Best Responses

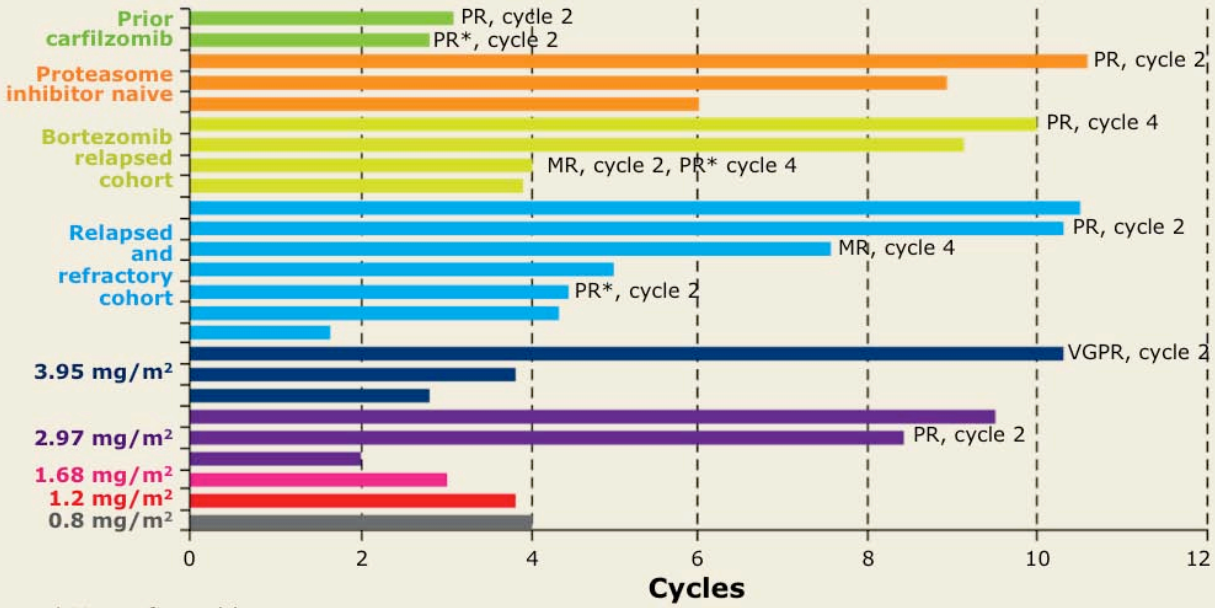
Response rate	All cohorts (n = 50)	Expansion cohort (n = 31)
ORR	9 (18%)	8 (26%)
VGPR	1 (2%)	0
Partial response	8 (16%)	8 (26%)
Minimal response	1 (2%)	1 (3%)
Stable disease	15 (30%)	NR

ORR = overall response rate; VGPR = very good partial response;
NR = not reported

Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

Research To Practice®

Duration of ≥Stable Disease with MLN9708

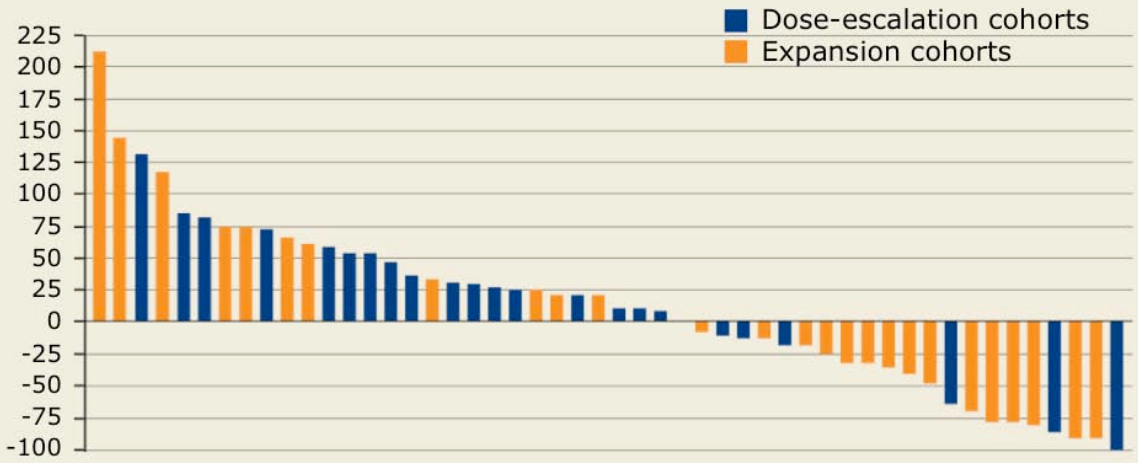


* Unconfirmed best response

With permission from Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

Research To Practice®

Patients' Best M-Protein Responses to Treatment with MLN9708

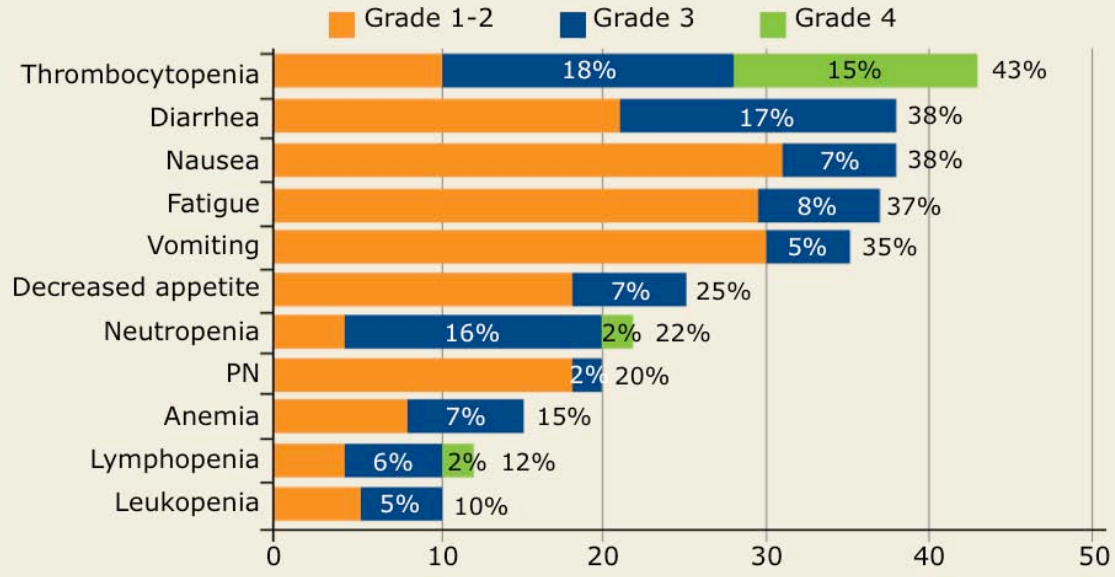


- Among 50 response-evaluable patients, 15 (30%) had M-protein reductions of ≥25%
  - 9 (18%) had best M-protein reductions of ≥50%, including 3 of ≥90% and 1 immunofixation-negative

With permission from Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

Research To Practice®

Drug-Related Adverse Events (AEs)*

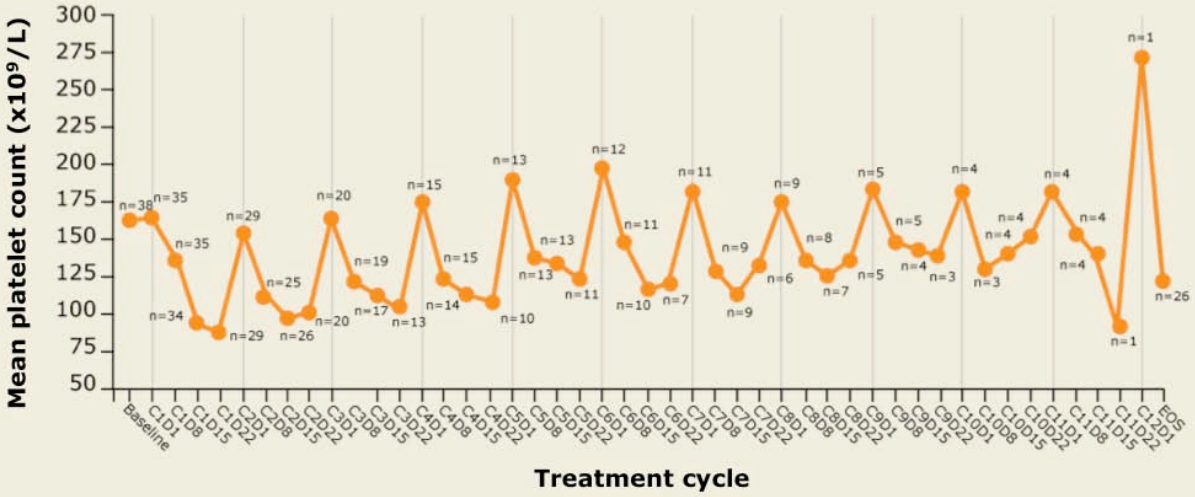


* ≥20% any grade or ≥5% Grade ≥3

With permission from Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

Research To Practice®

Thrombocytopenia



- Thrombocytopenia appeared to be transient and cyclical:
  - Platelet count recovered toward baseline in the rest period at the end of each cycle.
- Only 8% of patients required platelet transfusions.

With permission from Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

Research To Practice®

Author Conclusions

- Single-agent oral MLN9708 MTD was established as 2.97 mg/m^2 on a weekly (days 1, 8 and 15 q28d) dosing schedule.
- Oral MLN9708 was generally well tolerated.
  - AEs consisted mostly of hematologic and gastrointestinal events and were generally manageable, with a low rate of discontinuations
  - Infrequent peripheral neuropathy
- Pharmacokinetic profile supports weekly oral dosing (data not shown).
- Phase I data suggest clinical activity in relapsed and/or refractory MM (median 4 prior lines of therapy).
  - ORR (≥PR) of 18%, plus 2% MR and 30% SD
  - Responses seen in patients with prior exposure to proteasome inhibitors, including bortezomib

Kumar SK et al. *Proc ASCO* 2013;Abstract 8514.

Research To Practice®

Investigator Commentary: Phase I Trial of MLN9708 (Ixazomib) in Relapsed/Refractory MM

Oral MLN9708 is a major improvement on intravenous or even subcutaneous bortezomib (Btz). This Phase I study of weekly MLN9708 as a single agent managed to achieve a nice administration schedule with limited toxicity. I believe we may have an opportunity to use oral MLN9708 in the elderly, frail patient population.

MLN9708-associated thrombocytopenia is similar to that observed with Btz. A slight increase in mainly Grade 1 and 2 diarrhea also seems to occur with MLN9708. The gastrointestinal toxicities are a concern. They appear to be slightly increased compared to those seen with Btz. On the other hand, as with carfilzomib, peripheral neuropathy (PN) seems to be less of an issue with MLN9708 than with Btz. In this study, the rate of Grade 1 and 2 PN was 18% and the rate of Grade 3 and 4 PN was 2%.

The efficacy of MLN9708, to some extent, seems to be comparable to that of Btz. With single-agent MLN9708, 30% of patients experienced a 25% or higher reduction in M-protein and 24% experienced reductions of 50% or more. From the efficacy and safety point of view, oral MLN9708 has a good chance of making it into clinical practice in my opinion.

Interview with Antonio Palumbo, MD, August 12, 2013