5 Minute JournalClub

POST-ASH Issue 1, 2014

GEM2010MAS65: Sequential versus Alternating Bortezomib/Melphalan/ Prednisone and Lenalidomide/ Dexamethasone for Newly Diagnosed Multiple Myeloma

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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 up-front and maintenance therapeutic options in the treatment of multiple myeloma (MM) 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 lenalidomide in combination with low-dose dexamethasone (Rd) as an up-front therapeutic option for elderly patients with newly diagnosed MM, and consider this information for the treatment of patients.
- Compare and contrast the benefits and risks of bortezomib/melphalan/prednisone (VMP) and Rd for elderly patients with newly diagnosed MM when administered in a sequential versus an alternating manner.
- Assess the efficacy and safety of therapeutic regimens containing an alkylating agent versus those that do not for elderly, transplant-ineligible patients with newly diagnosed MM.
- Analyze the extended and updated results from the Phase III HOVON-65/GMMG-HD4 trial of bortezomib during induction and maintenance therapy for newly diagnosed MM, including outcomes of patients with renal failure.
- Evaluate the updated patient survival outcomes from the IFM 2005-02 study and the role of lenalidomide maintenance therapy after first-line autologous stem cell transplantation in MM.

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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: January 2014
Expiration date: January 2015

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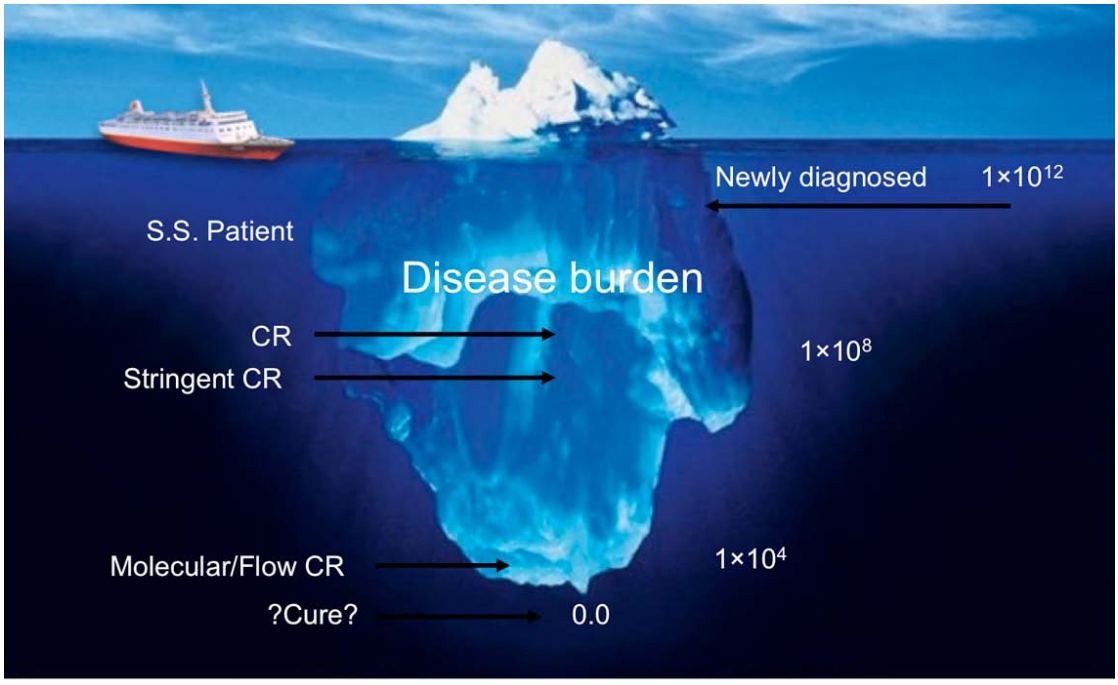
POST-ASH Issue 1, 2014

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

Sagar Lonial, MD

The revolution in myeloma therapy engendered by the development of proteasome inhibitors and immune modulatory drugs has not only changed the natural history of the disease but also has led some investigators to adopt a "more is better" treatment goal whereby efforts are made at diagnosis to maximally drive down the tumor burden and keep it suppressed for as long as possible. Dr Sagar Lonial is among the champions of this concept, and last week I chatted with him to further clarify his vision of this paradigm and better understand how it applies to evolving clinical research, especially new data emerging at ASH.

The fundamental idea behind this strategy is perhaps not that much different than what has been hypothesized for many cancers in the past. As depicted by the innovative "iceberg" graphic (see below) that Sagar has been using in many of his recent presentations, the goal is either a diffuse large B-cell lymphoma-like cure or a much longer duration of freedom from disease progression.



Getting to Minimal Residual Disease (MRD). Lonial, S. Reprinted with permission.

Assays to assess MRD are critical to this type of clinical research, and interestingly, Dr Lonial believes that the approach may be far less relevant in the relapsed/refractory setting, where many more mutant tumor clones have developed. The concept of prolonged disease suppression with some type of maintenance is also part of this strategy, and like a number of investigators Sagar often uses a variation of RVD maintenance, particularly in patients with higher-risk tumors.

Many oncologists — myself included — carry a hard-learned skepticism of the "more is better" paradigm from prior research in other tumors, including metastatic breast cancer, where a classic ECOG trial run by Dr George Sledge demonstrated the same survival with combination chemotherapy versus sequential single agents, and an important and vocal segment of myeloma investigators — particularly Dr S Vincent Rajkumar and his Mayo Clinic colleagues — have supported less intensive and better tolerated treatment choices in patients at standard risk. Both groups are committed to cure as a goal, but there is disagreement about what this all means to current practice, and even Sagar believes that with the available therapies a very small fraction of patients might be cured, even functionally, and he is particularly focused on patients with MRD negativity by new flow cytometry techniques along with PET scan normalization.

At the last ASCO meeting, Dr Lonial co-chaired the oral myeloma session and discussed several major up-front trials within the context of the iceberg model. We found his take on the issue to be quite provocative and as such attempted to recreate the format for the first issue of our annual post-ASH roundup. Here is his bottom line on the most noteworthy related oral papers from New Orleans mixed with Dr Lonial's perspectives:

1. FIRST trial (Phase III): MPT versus 18 months of lenalidomide/low-dose dexamethasone versus continuous Rd until disease progression in transplant-ineligible patients

Perhaps the most visible myeloma story out of ASH was this **largely European trial** that was afforded plenary status because in many parts of the world (unlike the US) where MPT is now utilized, this study will likely establish a new standard treatment as these data demonstrate superior PFS and OS in favor of continuous Rd versus MPT. However, perhaps even more relevant was the 38% statistically significant improvement in time to progression (32.5 versus 21.9 months) for continuous Rd as opposed to 18 months, though it may be too early to evaluate OS. This long-term treatment strategy is in keeping with (and may ultimately provide support for) Dr Lonial's notion to proactively attempt to delay disease progression.

2. Other trials of up-front management

Not surprisingly, **Dr Antonio Palumbo** was again on stage at ASH presenting yet another Phase III trial of up-front treatment, this time evaluating Rd versus MPR versus

cyclophosphamide/prednisone/lenalidomide (CyPR) in elderly patients not eligible for transplant. Building off the FIRST trial, all 3 arms of this effort yielded comparable disease-related outcomes in terms of PFS and overall response rates. Of note, patients receiving melphalan experienced more treatment-related toxicity than those receiving cyclophosphamide, and Dr Lonial sees this as one more reason that in myeloma the end may be near for melphalan.

Another important up-front trial — **HOVON-65/GMMG-HD4** — reported more follow-up at ASH. This study, which had previously demonstrated an advantage to bortezomib with doxorubicin/dex induction therapy followed by bortezomib maintenance versus vincristine with doxorubicin/dex followed by thalidomide maintenance, continues to yield a PFS and OS benefit for the bortezomib-based regimen, and the update provides further support for the use of this proteasome inhibitor in patients with renal failure and adverse risk factors. The study used a bortezomib maintenance schedule of 1 dose every other week for 2 years, but Dr Lonial notes that subcutaneous maintenance bortezomib may be even more patient friendly, and oral proteasome inhibitors such as ixazomib and oprozomib might further facilitate this strategy.

Finally, a paper by **Mateos et al** investigated the novel induction strategy of alternating Rd with VMP in elderly patients. Although Dr Mateos and her colleagues conclude that the alternating scheme is superior in efficacy versus the sequential approach, it is difficult to compare this regimen to the 3- and 4-drug combinations currently used in practice. In keeping with his intent to achieve rapid and deep responses even in older patients (with tolerable regimens), Dr Lonial favors the combination approach.

3. More data on lenalidomide maintenance

Of the 3 major Phase III trials of len maintenance, two — CALGB-100104 and the Italian MM-015 study — have demonstrated a survival benefit, and this led to a major shift in US practice. However, the **third study** from the French IFM group (IFM 2005-02), which was updated at ASH, continues to show a substantial PFS benefit without improvement in OS. In discussing this data set, Dr Lonial noted that part of this discrepancy may be related to the IFM 2005-02 trial's design, in which all patients received 2 months of post-transplant lenalidomide consolidation, including those randomly assigned to "no maintenance." Another critical difference is that the IFM stopped len maintenance treatment at 2 years as opposed to indefinite therapy until disease progression/toxicity in the other 2 studies.

Also at ASH we saw findings from a **meta-analysis** of lenalidomide maintenance, demonstrating a PFS and OS benefit. However, Dr Lonial found it difficult to dissect out the relevance of this data set because it included patients who did and did not receive a transplant. The study did, however, provide some additional insight about the incidence of second primary cancers, which to this point appears to be mainly a modest risk of hematologic neoplasms, including AML and MDS.

Although the “more is better” investigators have focused on current regimens with approved agents, it is likely that completely different classes of drugs will be required to melt away substantially more of the iceberg, and in another myeloma issue in this series we will attempt to pick out the agents farthest along in this desperate race, including monoclonal antibodies and filanesib — a fascinating kinesin spindle protein inhibitor reported at ASH by Dr Lonial’s group to cause responses (as a single agent and with low-dose dex) in patients refractory to conventional agents. Next on this series, an ASH CML update including the current status of ponatinib.

Neil Love, MD
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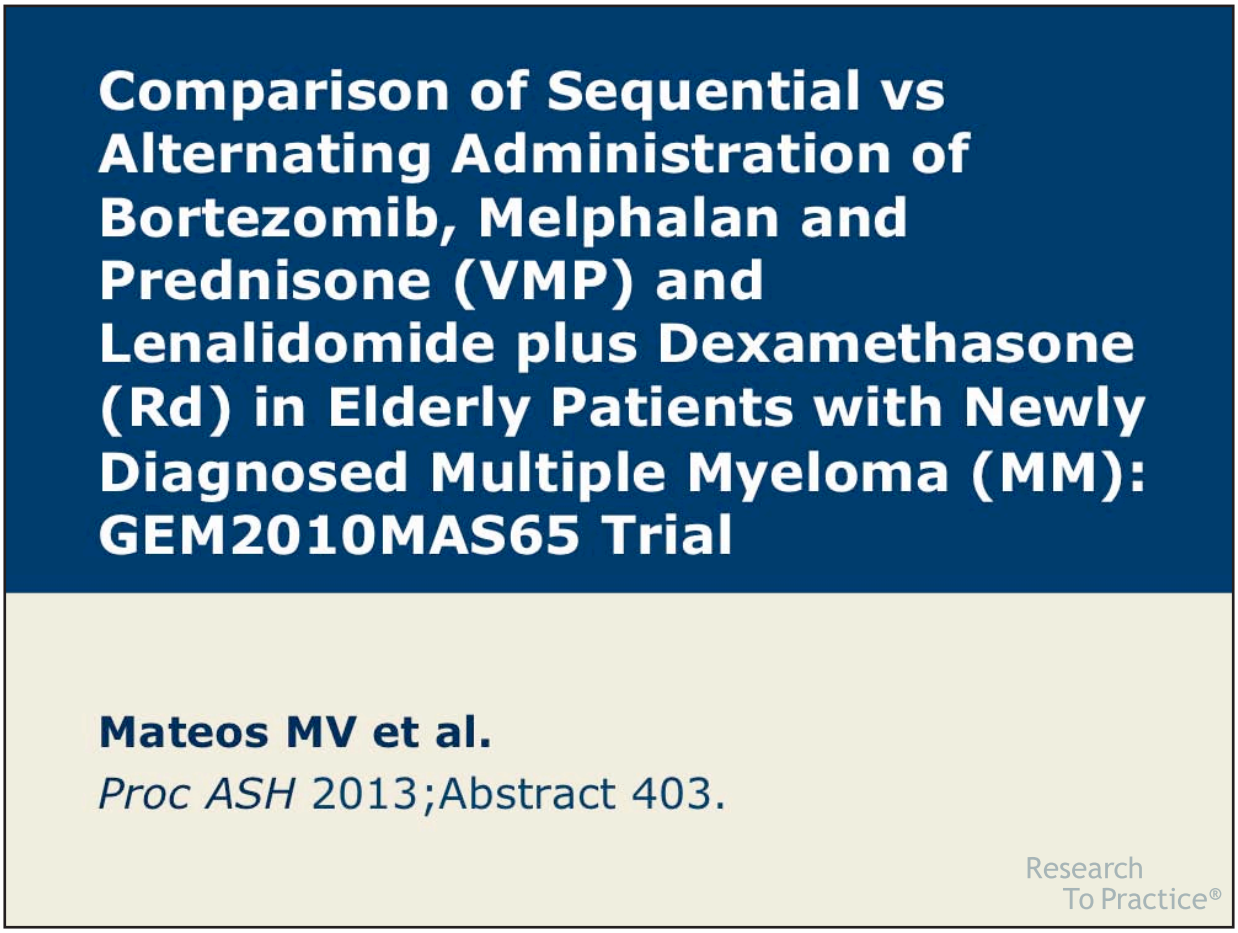
GEM2010MAS65: Sequential versus Alternating Bortezomib/ Melphalan/Prednisone and Lenalidomide/Dexamethasone for Newly Diagnosed Multiple Myeloma

Presentation discussed in this issue

Mateos MV et al. **Comparison of sequential vs alternating administration of bortezomib, melphalan and prednisone (VMP) and lenalidomide plus dexamethasone (Rd) in elderly patients with newly diagnosed multiple myeloma (MM): GEM2010MAS65 trial.** *Proc ASH* 2013;**Abstract 403**.

Slides from a presentation at ASH 2013 and transcribed comments from a recent interview with Sagar Lonial, MD (1/22/14)



Background

- Two of the most efficient regimens for the treatment of newly diagnosed MM in elderly patients are bortezomib/melphalan/prednisone (VMP) and lenalidomide/low-dose dexamethasone (Rd) (*JCO* 2013;31(4):448; *Proc ASH* 2013;Abstract 2).
  - To further improve outcomes in this patient population, a possibility would be the simultaneous administration of all drugs in these regimens, but this may result in high toxicities.
  - The administration of VMP and Rd in a sequential or alternating manner could improve outcomes with acceptable toxicity.
- **Study objective:** To compare the efficacy and safety of VMP and Rd when administered in a sequential versus alternating manner in elderly patients with newly diagnosed MM.

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

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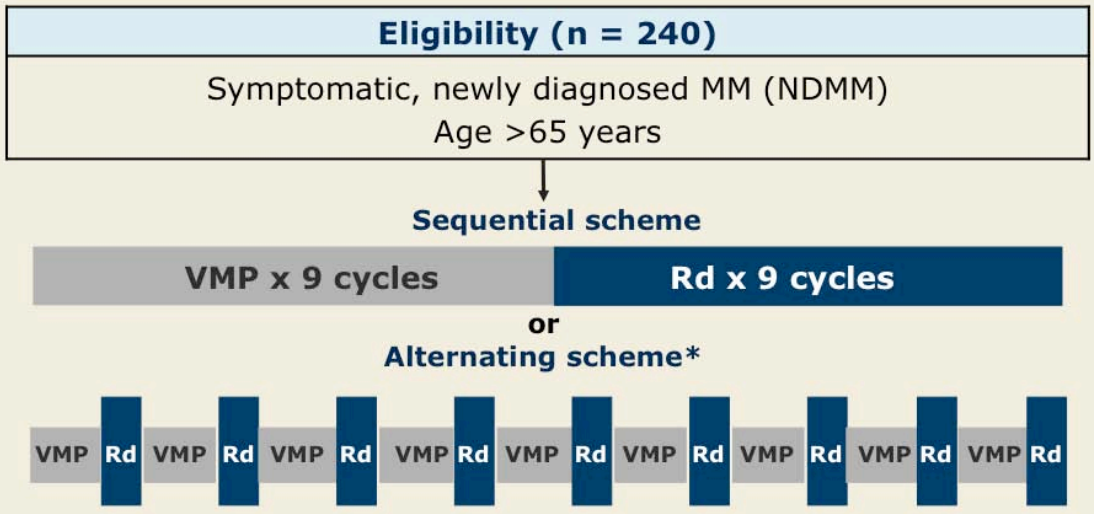
GEM2010MAS65 Phase II Trial Design



* Half of the patients start with VMP and half with Rd.

- Treatment duration: 74 weeks

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

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Response Rates After 9 Cycles

	Sequential (n = 86)	Alternating VMP and Rd (n = 86)
Overall response rate (ORR)	89%	93%
Stringent CR (sCR)	5%	11%
Complete response (CR)	21%	30%
Very good PR (VGPR)	30%	37%
Partial response (PR)	33%	15%
Stable disease (SD)	6%	5%
Progressive disease	5%	0%

- Significant differences between the sequential and alternating arms in the rate of sCR/CR/VGPR (p = 0.004) and the rate of sCR/CR (p = 0.02)
- No significant difference between VMP → Rd and Rd → VMP

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

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Response Rates in the Intention-to-Treat Population*

	Sequential (n = 117)	Alternating (n = 114)
ORR	89%	94%
sCR	12%	22%
CR	27%	24%
VGPR	21%	23%
PR	29%	25%
SD	7%	4%
Not evaluable	4%	2%

* After a median of 13 cycles (range: 1-18)

- Sequential vs alternating arms, sCR/CR/VGPR (p = 0.1); sCR/CR (p = 0.2)
- 33% of patients in CR in each arm achieved immunophenotypic CR
- No significant difference between VMP → Rd and Rd → VMP

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

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Efficacy According to Cytogenetic Abnormalities

	Standard risk		High risk	
	Sequential (n = 77)	Alternating (n = 83)	Sequential (n = 19)	Alternating (n = 14)
sCR/CR	40%	44%	47%	42%
VGPR	18%	13%	37%	28%
PR	31%	28%	11%	21%

High-risk cytogenetics: t(4;14), t(14;16), del17p

- No significant difference between the 2 alternating treatment arms

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

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Survival Rates at 20 Months

Survival outcome	Sequential	Alternating	
		VMP → Rd	Rd → VMP
PFS*	80%	92%	75%
OS*	88%	96%	88%
PFS by response	**Sequential†**	**Alternating†**	
sCR/CR	92%	96%	
≤VGPR	62%	78%	
OS by response	**Sequential†**	**Alternating**	
sCR/CR	100%	93%	
≤VGPR	80%	90%	

* No significant difference between arms; † Statistically significant difference between response types

- No PD in patients who achieved immunophenotypic CR

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

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Efficacy in Patients with Poor Prognostic Characteristics

Characteristic	sCR/CR	PFS at 20 months	OS at 20 months
Age <75 years	47%	88%	94%
Age ≥75 years	37%*	77%	84%†
ISS Stage I/II	42%	85%	93%
ISS Stage III	42%	84%	83%
No adverse cytogenetics	42%	84%	92%
t(4;14), t(14;16), 17p, 1q+	48%	87%	90%
t(4;14), t(14;16), 17p	45%	82%	82%

* CR rate in the sequential arm in patients <75 vs ≥75 years was 49% vs 29% (p = 0.01)

† A significant difference was observed in both sequential and alternating arms

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

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Select Grade 3/4 Adverse Events

Hematologic*	Sequential (n = 117)	Alternating (n = 114)
Anemia	2%	5%
Neutropenia	14%	24%
Thrombocytopenia	16%	20%
Nonhematologic*		
Infections	6%	7%
Skin rash	5%	4%
GI toxicity	6%	6%
Peripheral neuropathy	6%	3%
Deep vein thrombosis	2%	2%

* No significant different between arms

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

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Author Conclusions

- Therapeutic regimens including an alkylating agent, a proteasome inhibitor and an immunomodulatory agent, whether administered in a sequential or alternating approach, are effective and well tolerated by elderly patients.
- After 9 induction cycles, the alternating scheme is superior in efficacy, especially in terms of sCR/CR versus the sequential scheme, without additional toxic effects.
- Patients who achieve CR have a better outcome.
- The benefit of these combinations seems to be consistent in different risk groups, especially in patients with high-risk cytogenetic abnormalities.
- A longer follow-up period is required to evaluate the final benefit of the alternating versus sequential VMP and Rd schemes based on a total therapy approach for elderly patients with MM.

Mateos MV et al. *Proc ASH* 2013;Abstract 403.

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Investigator Commentary: Efficacy and Safety of Sequential versus Alternating VMP and Rd for Elderly Patients with NDMM

This study was based on the hypothesis that administering VMP and Rd in an alternating scheme would result in higher efficacy because of earlier access to all the agents in both regimens.

In the sequential scheme, with disease that is more sensitive to an immunomodulatory drug (IMiD) than to a proteasome inhibitor, the effect of the IMiD would not be achieved until after 9 cycles of therapy. By alternating the regimens, exposure and response to the IMiD would occur earlier.

Alternating the regimens was undertaken in an effort to reduce toxicity. I usually take a more aggressive approach and would administer a combination of 3 or even 4 agents. The exception to using that approach is with patients who are frail and would not tolerate aggressive therapy.

Interview with Sagar Lonial, MD, January 22, 2014

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