# 5 Minute JournalClub

***Key ASH Presentations***
Issue 7, 2011

# Subcutaneous versus Intravenous Administration of Bortezomib in Multiple Myeloma

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## 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 from a plethora of ongoing clinical trials 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 and other cancer clinicians in the formulation of optimal clinical management strategies for hematologic cancer.

## LEARNING OBJECTIVES

- Compare and contrast the efficacy and safety outcomes with subcutaneous versus intravenous bortezomib administration in multiple myeloma.
- Counsel patients with multiple myeloma about the known benefits and risks of bortezomib when administered subcutaneously and intravenously.

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**Click here for papers on proteasome inhibitors and IMiDs in multiple myeloma**

In the last issue of our San Antonio-focused edition of this series, we opined about the lack of recent research progress in breast cancer and looked to a tumor occurring at one tenth the frequency for inspiration and hope. Multiple myeloma affects approximately 20,000 new patients in the US annually and for a long time was a disease stuck for new therapeutic options. However, fairly recently two classes of treatments have stormed onto the scene — immunomodulatory agents (IMiDs) and proteasome inhibitors — making myeloma perhaps the fastest moving and most dynamic area in oncology.

It's difficult to figure out exactly what led to this encouraging state of affairs, but those in the middle of it all claim that an effective partnership between academia, industry and unusually active advocacy groups made it happen. One might also consider that perhaps there was a unique and fortunate tumor biopharmacology at work here. Regardless of the source of this important progress, currently, lenalidomide, bortezomib and to a lesser extent thalidomide are helping patients with myeloma live longer and feel better. Perhaps even more importantly, two exciting but not yet approved agents — carfilzomib and pomalidomide — seem poised to further transform the classic paradigms of this enigmatic disease. Several related ASH data sets provide a glimpse of what the future may hold for these unique classes of agents:

1. **Subcutaneous bortezomib**

A large (n = 222) international Phase III study demonstrated similar efficacy but markedly less neurotoxicity when SC bortezomib was compared to IV administration in the refractory setting. These intriguing findings suggest that higher peak drug levels occurring with IV treatment may correlate with neuronal damage and that the SC approach may offer obvious patient care advantages. Investigators are very quickly attempting to further validate this interesting concept. Another important clinical research avenue with bortezomib as presented by Antonio Palumbo and others is weekly dosing of the agent, which seems to be equally efficacious and much less neurotoxic

2. **Pomalidomide**

Two more Phase II studies of this fascinating and well-tolerated IMiD combined with dexamethasone demonstrated substantial antitumor effect in almost half of the trial participants, all of whom were considered refractory to both bortezomib and lenalidomide. Clinicians seem ready to use this drug now.

3. **Carfilzomib**

Again, significant activity was seen in later-line treatment in two separate Phase II studies, with minimal neurotoxicity, including a lack of worsening of this challenging adverse effect in patients with baseline peripheral neuropathy. A current compelling Phase III study is randomly assigning patients to either CRD or Rd in the search for the "R-CHOP" of myeloma. As with pomalidomide, oncologists again seem ready and interested in utilizing this agent.

Next up on our final ASH *5-Minute Journal Club*: Papers on MDS, AML and my personal favorite current topic in oncology, AP.

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**Research To Practice**
Miami, Florida

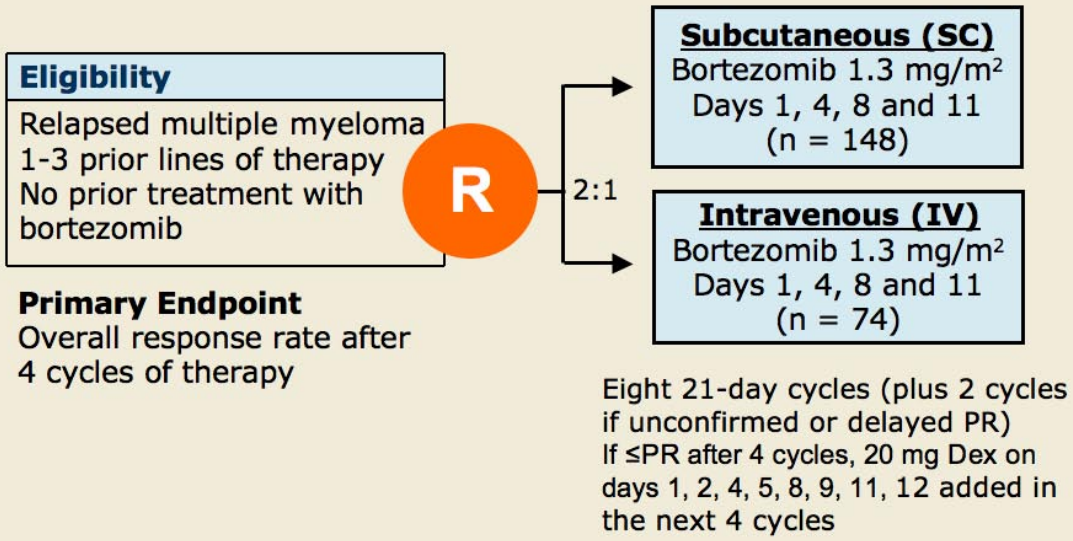
# Subcutaneous versus Intravenous Administration of Bortezomib in Multiple Myeloma

## Presentation discussed in this issue

Moreau P et al. **A phase 3 prospective, randomized, international study (MMY-3021) comparing subcutaneous and intravenous administration of bortezomib in patients with relapsed multiple myeloma.** *Proc ASH* 2010;**Abstract 312**.

## Slides from a presentation at ASH 2010 and transcribed comments from a recent interview with Rafael Fonseca, MD (12/22/10)

# Phase III Multicenter Trial Schema




Moreau P et al. *Proc ASH* 2010;Abstract 312.

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# Treatment Exposure

| | Bortezomib SC (n = 147)* | Bortezomib IV (n = 74) |
|---|---|---|
| Number of Cycles (Median) | 8 | 8 |
| Time on Study Drug (Median) | 22.57 weeks | 22.57 weeks |
| Cumulative Bortezomib Dose (Median) | 33.76 mg/m² | 31.46 mg/m² |
| Patients Receiving Dexamethasone | 56% | 53% |

* Data shown for safety population. One patient in the SC arm was not treated.

Moreau P et al. *Proc ASH* 2010;Abstract 312.

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# Clinical Responses After Four Cycles

| | Bortezomib SC (n = 145) | Bortezomib IV (n = 73) |
|---|---|---|
| Overall Response Rate[1] | 42% | 42% |
| Complete Response (CR) | 6% | 8% |
| Partial Response (PR) | 36% | 34% |
| ≥Very Good PR (VGPR) | 17% | 16% |

[1] Relative risk of overall response rate is 0.99 with 95% confidence interval of 0.71-1.37

Moreau P et al. *Proc ASH* 2010;Abstract 312.

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# Additional Efficacy Outcomes

| In Responding Patients | Bortezomib SC (n = 76) | Bortezomib IV (n = 38) |
|---|---|---|
| Time to First Response (Median) | 1.4 mos | 1.4 mos |
| Time to Best Response (Median) | 1.6 mos | 1.5 mos |
| Duration of Response (Median) | 9.7 mos | 8.8 mos |

| Intent-to-Treat Population | Bortezomib SC (n = 148) | Bortezomib IV (n = 74) |
|---|---|---|
| Time to Disease Progression (Median) | 10.4 mos | 9.4 mos |
| One-Year Survival Rate | 72.6% | 76.7% |

Moreau P et al. *Proc ASH* 2010;Abstract 312.

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# Select Adverse Events

| | Bortezomib SC (n = 147) | Bortezomib IV (n = 74) | *p*-value |
|---|---|---|---|
| Grade ≥3 Adverse Events | 57% | 70% | — |
| Grade 3/4 Anemia | 14% | 12% | — |
| Grade 3/4 Leukopenia | 8% | 18% | — |
| Peripheral Neuropathy (All Grades) | 38% | 53% | 0.04 |
| Grade ≥3 Peripheral Neuropathy | 6% | 16% | 0.03 |

Moreau P et al. *Proc ASH* 2010;Abstract 312.

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# Author Conclusions

- The efficacy of bortezomib is similar by SC and IV administration in patients with relapsed MM.
- The PK-PD profiles of SC and IV bortezomib are similar (data not shown).
- SC administration of bortezomib appears to have an improved safety profile with respect to peripheral neuropathy compared to IV administration.
- SC administration has acceptable local tolerability (data not shown).

Moreau P et al. *Proc ASH* 2010;Abstract 312.

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## Investigator comment on subcutaneous versus intravenous administration route for bortezomib in multiple myeloma

This is definitely exciting as it makes it more convenient for the patients, who may not have to have an IV line placed for bortezomib infusions. Based on this study, the subcutaneous route of administration of bortezomib appears to be at least as effective, if not potentially even better than, the intravenous route. The data even show a lower rate of peripheral neuropathy and ≥Grade 3 adverse events.

This opens a new door for a more convenient treatment for patients with myeloma, many of whom have difficulties with mobility and access to the clinic. Even self-administration approaches could be explored without any compromise in tolerability. Hopefully this will be adopted as a standard approach as more information comes forward.

***Interview with Rafael Fonseca, MD, December 22, 2010***

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