

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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## Update on Proteasome Inhibitors in Multiple Myeloma



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### H&O Which proteasome inhibitors are available or in development?

**PGR** The number of proteasome inhibitors is expanding. The first agent in this class was bortezomib (Velcade, Millennium Pharmaceuticals), which received approval from the US Food and Drug Administration (FDA) for use in multiple myeloma as a third-line treatment in 2003, second-line treatment in 2005, and first-line treatment in 2008. The agent was also approved for use as a second-line treatment in mantle cell lymphoma in 2006. In 2012, subcutaneous administration was approved for all approved indications.

The next proteasome inhibitor to receive approval was carfilzomib (Kyprolis, Onyx), in 2012. This was the first of the second-generation agents, which was an exciting advance. Carfilzomib had increased potency compared with bortezomib and irreversible binding on the target. In addition, preclinical data suggested that carfilzomib might be active in the face of bortezomib resistance. Carfilzomib was awarded accelerated approval for patients with multiple myeloma whose disease has progressed after receiving at least 2 prior therapies, including bortezomib and an immunomodulatory agent. Contingent on the results of recently completed phase 3 combination trials, carfilzomib is likely to obtain full approval soon.

In addition, several proteasome inhibitors are being studied that hopefully will receive FDA approval over the next few years. These include the orally bioavailable

agents ixazomib, oprozomib, and marizomib. Ixazomib in particular shows great promise, especially in combination with lenalidomide and dexamethasone; it is now in several phase 3 trials.

### H&O What are some of the important differences between these agents?

**PGR** One obvious difference is that ixazomib and oprozomib are oral agents, whereas bortezomib and carfilzomib are administered either subcutaneously or intravenously. Furthermore, proteasome inhibitors in clinical use encompass a broad scope of drugs that have important mechanistic differences. Specifically, bortezomib and ixazomib are peptide boronates, carfilzomib and oprozomib are epoxyketones, and marizomib is a  $\beta$ -lactone.

Peptide boronates work by reversibly targeting the  $\beta$  subunits of the proteasomal apparatus, and inhibit the proteasome as a result. Epoxyketones, by contrast, irreversibly inhibit the proteasome by covalently binding to the  $\beta$  subunits—as does the  $\beta$ -lactone marizomib. Interestingly, while carfilzomib binds both  $\beta$ -1 and  $\beta$ -2 subunits, marizomib appears to bind all 3  $\beta$  subunits and has the most potency and the broadest effect in vitro to date. In this context, we rely on the regeneration of the proteasome in both epoxyketones and  $\beta$ -lactones to restore normal tissue activity, and so hope to exploit a therapeutic index accordingly.

## H&O Could you talk about the advantages and disadvantages of these agents?

**PGR** Bortezomib has a well understood and manageable safety profile, especially when administered subcutaneously. It is rarely associated with significant adverse cardiac or pulmonary side effects, and it is a very good choice for multiple myeloma patients with kidney dysfunction. However, a common side effect of bortezomib is neuropathy, which can be dose limiting. Although we have become much better at managing this side effect, an important improvement as mentioned earlier was the introduction of subcutaneous administration in 2012. Subcutaneous administration has been shown to work just as well and cause less neuronal injury compared with intravenous use, which of course can still be used if preferred.

In terms of other peptide boronates, ixazomib has a more rapid-on/rapid-off pharmacology that makes it more specific than bortezomib to tumor cells. As a result, ixazomib has a potentially improved therapeutic index. The drug does cause skin rash, which is generally manageable, but it has only mild to moderate gastrointestinal toxicity. In fact, the favorable tolerability profile of ixazomib makes it an ideal drug to use for maintenance treatment as well as in combination treatment. Of course, it also has the advantage of being an oral medication rather than an injectable one. Large trials with lenalidomide and dexamethasone are now under way in various settings, as described previously. The fact that all-oral regimens are being tested that combine proteasome inhibitors with immunomodulatory compounds makes these truly landmark studies.

The big advantage of carfilzomib (as an irreversible epoxyketone proteasome inhibitor) over the boronate peptide class is that it appears to be more potent. Of particular note, carfilzomib only rarely produces neuropathy. Side effects of carfilzomib also include cardiac, pulmonary, and renal effects, which are uncommon, along with fatigue and thrombocytopenia, which are more common. Generally speaking, however, carfilzomib is well tolerated, and it can be effective when bortezomib has failed.

Oprozomib is similar to carfilzomib, but like ixazomib it can be given in oral form, which also makes it a very exciting option with considerable potential. One disadvantage is that it causes significant gut toxicity, which can be dose limiting, as well as other side effects, including fatigue and low platelet counts, which are generally manageable with supportive care. Nonetheless, we await future studies of this agent with great interest.

Marizomib, a  $\beta$ -lactone, has the advantage of being the most potent agent studied so far. Like carfilzomib, marizomib can overcome bortezomib resistance and is especially active preclinically as part of combination

treatment. Single-agent studies have been encouraging, with responses seen in patients with highly resistant and advanced disease. Side effects have included fatigue, thrombocytopenia, and transient central nervous system toxicity characterized by mild confusion and occasional headache. As with carfilzomib, caution is needed in patients with renal dysfunction, and peripheral neuropathy is very uncommon. Importantly, there has been no significant cardiac toxicity to date.

## H&O How has the role of proteasome inhibitors evolved in multiple myeloma?

**PGR** The uses for these agents have dramatically expanded, with their role as “backbone” agents truly validated in numerous trials. The ability to be selective for both resistance and tolerability, in addition to now having the convenience of oral administration, represents remarkable progress for this drug class as a whole.

## H&O Could you talk about your studies with ixazomib?

**PGR** In 2012, my colleague Dr Shaji Kumar presented on our behalf the results of our phase 1/2 trial with weekly ixazomib citrate (MLN9708) in combination with lenalidomide and dexamethasone at the American Society of Hematology (ASH) meeting. (Ixazomib citrate hydrolyzes to ixazomib [MLN2238], the biologically active form of the drug.) This study included 65 patients with previously untreated multiple myeloma who received 3 weekly doses of ixazomib citrate per 28 days in combination with lenalidomide (Revlimid, Celgene) and dexamethasone, for up to 12 cycles. Patients also received maintenance therapy with monthly ixazomib citrate until the disease progressed. Patients could discontinue treatment for autologous stem cell transplant after six 28-day cycles.

Side effects included fatigue, rash, nausea, and vomiting, all of which proved generally manageable with supportive care and dose reduction.

After a median follow-up of approximately 4 months, the overall response rate was 88%, including very good partial responses in 40% of patients and complete responses in 18%. Of the 50 patients who received at least 4 cycles of therapy, the overall response rate was encouraging at 96%, with very good partial responses in 44% of patients and complete responses in 26%.

At the most recent ASH meeting in December of last year, we presented our phase 1/2 results with twice-weekly oral ixazomib citrate in combination with lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma. This study included 64 patients, with transplant-

eligible patients being able to discontinue treatment for autologous stem cell transplant after 8 or more cycles.

The majority of patients—77%—received 8 or more cycles, and 20% received 16 or more cycles. The discontinuation rate was relatively low, at 14%.

Among the 58 patients who were evaluable for response, 93% had a partial response or better and 67% had a very good partial response or better, including a 24% complete response rate and a 14% stringent complete response rate, which is especially encouraging.

The analysis of minimal residual disease (MRD) was particularly exciting. Among 11 complete response patients analyzed, 9 were negative for MRD, for an MRD-negative rate of 82%. As impressive as this is, the caveat is that the total number of patients remains small.

A total of 14% of the participants discontinued their regimen because of side effects. This rate is relatively low, and of course it applies to all 3 drugs. Most of the side effects, including low blood cell counts, were consistent with what we see with lenalidomide and dexamethasone. The main exception was skin rash, which is associated with ixazomib citrate. Although most of the side effects were manageable, we found that the rates of rash and treatment-related peripheral neuropathy were lower with the weekly regimen than with the twice-weekly regimen. As a result, we are now pursuing a phase 3 trial with the weekly regimen.

Having said that, the twice-weekly combination is feasible and very active. What we may see in the future and subsequent to approval is that patients at high risk might receive twice-weekly therapy, at least to start with, followed then by a weekly regimen, for example.

### H&O What are the most important studies that have been conducted with oprozomib and marizomib?

**PGR** So far these studies have all been phase 1 and relatively limited in number, although marizomib was evaluated in a large US study and a good-sized Australian trial.

### H&O Is there anything you would like to add about proteasome inhibitors, and in particular ixazomib?

**PGR** It is very exciting to now have all-oral regimens that can be given as initial treatment and to see such a high quality of responses. Moreover, we are seeing both favorable tolerability and durable clinical benefit with the second-generation agents.

Specifically, I think ixazomib provides a paradigm of the improvements we want to see. In summary, if we can improve outcomes, keep side effects to a minimum, and make the regimen easier for the patient through the use of all-oral agents, that is a success. Ixazomib-based approaches, as an example, appear to be meeting this goal.

### Suggested Readings

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