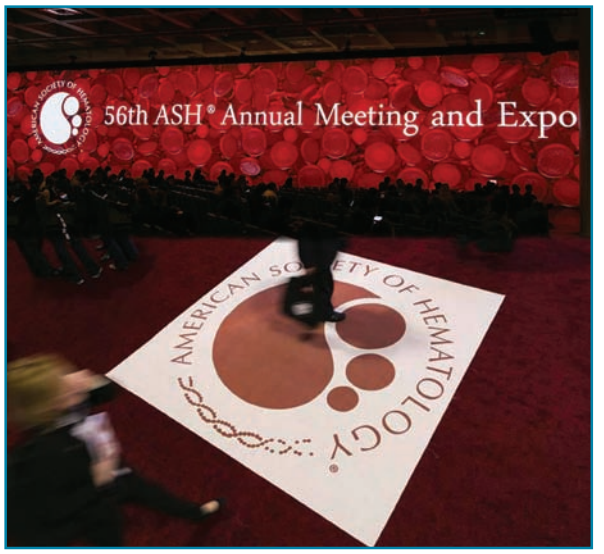
Multiple Myeloma: Oral Proteosome Inhibitor Ixazomib Moves from Induction to Maintenance

BY ROBERT H. CARLSON

SAN FRANCISCO—The value of maintenance therapy in treating hematological malignancies is being weighed in many arenas, but compliance is a concern.

In multiple myeloma, the proteosome inhibitor bortezomib has a solid place in several regimens but it is administered subcutaneously—certainly more convenient than intravenous administration as when the drug was first introduced—but patients still have to return to the clinic for weekly injections.

Now, though, a Phase II study of the safety and tolerability of the first oral proteosome inhibitor, ixazomib (MLN-9708), showed an increasing depth of response with long-term use following an all-oral induction regimen of ixazomib-lenalidomide-dexamethasone in patients with previously untreated multiple myeloma, as reported here at the American Society of Hematology Annual Meeting (***Abstract 82***).



"The takeaway message is that we have a completely oral triplet regimen for treating myeloma and that this new drug can be given on a long-term basis that potentially provides long-term disease control," said Shaji K. Kumar, MD, Professor of Medicine at Mayo School of Medicine, who presented the results, speaking in an interview before the meeting.

"The field is moving towards more prolonged treatment of multiple myeloma. The old concept was that we would treat the disease for x number of cycles, or months, and then stop and watch. But increasingly we are learning that a subgroup of patients may benefit from continuing treatment for a prolonged time—maybe two to three years, or even until progression."

Weekly ixazomib plus lenalidomide-dexamethasone had been investigated earlier in a Phase I/II trial as triplet induction therapy followed by single-agent ixazomib maintenance therapy. The new report covers Phase II efficacy and safety data in patients receiving ixazomib maintenance.

Study Details

A total of 50 patients were enrolled, with 29 discontinuing during induction, primarily to undergo stem cell transplant (14 patients), due to adverse events (6 patients), or patient withdrawal (4 patients).

Twenty-one patients received ixazomib maintenance therapy, and the median treatment duration for both induction and maintenance was 26.6 months.

Among the 49 evaluable patients, 44 (90%) achieved at least a partial response or better, including 29 (59%) who had very good or better responses.

"All 21 patients who received ixazomib maintenance had responded to induction therapy," Kumar said. Overall responses in the 21 patients included complete responses in 11 (52%).

During maintenance, 33 percent of patients improved their response, including two very good partial responses that improved to near complete response, and five very good partial responses that improved to complete response.

Kumar noted that there is a lot of experience with bortezomib-lenalidomide-dexamethasone, one of the most effective combinations, as well as with combined carfilzomib and lenalidomide-dexamethasone, which is also very effective: "So it made sense to examine how ixazomib would combine with lenalidomide and dexamethasone in a completely oral combination."

Oral ixazomib, therefore, he said, avoids the inconvenience of bortezomib, part of the backbone for many myeloma treatment regimens, which is given by subcutaneous injection once a week.

"Clearly there was a great need for an oral proteosome inhibitor, especially given the fact that the other major class of drugs for multiple myeloma, immunomodulatory drugs like lenalidomide and pomalidomide, are oral drugs taken once a day," Kumar said. "Ixazomib is the first to fill in that space.

"These data indicate that single-agent ixazomib maintenance for up to one and a half years was feasible and generally well tolerated, improved responses following ixazomib-lenalidomide-dexamethasone induction, and contributed to durable responses with a median of more than two years in previously untreated myeloma patients not undergoing stem cell transplant."

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Paul Richardson: 'Reassuring Tolerability'

Paul Richardson, MD, Director of the Myeloma Program at Dana-Farber Cancer Institute and the study's senior author and the moderator of the oral session where the paper was presented, called the data "extraordinary" and the tolerability "very reassuring."

Selecting Out Patients

Another expert, Saad Usmani, MD, Director of Clinical Research in Hematologic Malignancies and Head of the Myeloma Program at Levine Cancer Institute, was asked for his perspective for this article: "If you can prove equal or better efficacy without a lot of side effects, then oral medicines make sense," he said, noting, though, that patients in the trial were not bortezomib refractory or resistant, and the study researchers selected out patients who were not exposed to or had not become resistant to proteasome inhibitors.

"I think that's the key feature," he said.

The oral availability aspect is important, he said, "but you are selecting out patients who may still be sensitive to proteasome inhibition."

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