

# Multiple Myeloma: How to Fit the Three New Drugs into Clinical Practice

BY MARK L. FUERST

ORLANDO, Florida—A panel of experts from the Food and Drug Administration and two prominent myeloma experts explained how three multiple myeloma drugs—daratumumab, ixazomib, and elotuzumab—received approval in the last three weeks and how these drugs can be incorporated into community practice. The discussion took place here at the American Society of Hematology Annual Meeting at an ASH/FDA Joint Symposium on Late Breaking Drug Approvals.

The FDA approved 18 “Fast Track” products in the last year, and gave 17 drugs or indications Breakthrough Therapy status in the last two years, including daratumumab and elotuzumab, noted the session’s moderator, Albert B. Deisseroth, MD, PhD, Medical Officer in the FDA’s Office of Hematology and Oncology Products. After Priority Review, all three of the new drugs were approved within three to four months of submission of market applications.

Among those speaking, **S. Vincent Rajkumar, MD**, Professor of Medicine at the Mayo Clinic, said: “We have witnessed unprecedented change in multiple myeloma. Three amazing drugs were approved rapidly. We are fortunate in the U.S. that we can afford to approve these drugs. Many more drugs are in the pipeline. The best is yet to come.”



## ‘Very Heterogeneous’

He explained that multiple myeloma is very heterogeneous, and is probably actually six or seven diseases: “The aggressiveness of the disease varies based on the genetic type,” and the revised International Staging System guidelines take into account host characteristics, tumor burden, and disease aggressiveness.

For initial treatment, the most important change is the establishment of levels of the combination of

lenalidomide and dexamethasone, he said. “The FIRST trial showed that lenalidomide-dexamethasone replaces melphalan-based initial therapy. Progression-free survival is significantly better, and overall survival is superior.”

Bortezomib also prolongs progression-free and overall survival in frontline therapy, and there are numerous frontline treatments now available for multiple myeloma patients. “We have 22 possible recommended regimens, which does lead to confusion in the community,” Rajkumar said.

He noted that the results of a trial presented earlier during the ASH meeting provided more clarity on how to treat newly diagnosed patients: The randomized, Phase III SWOG SO777 trial (*Durie et al, Abstract 25*) showed that the addition of bortezomib to lenalidomide and dexamethasone for induction therapy in previously untreated myeloma results in a statistically significant and clinically meaningful improvement in both progression-free and overall survival. With an acceptable safety and tolerability profile, despite increased neurotoxicity, this regimen represents a potential new standard of care.

Many oncologists in the United States are already using this regimen, Rajkumar said. “This regimen can be used in patients who are non-transplant or transplant candidates. The introduction of new drugs means we may no longer need to send patients to transplant.”

He noted that the IFM/DFCI 2009 trial found that early transplantation led to prolonged progression-free survival, although the overall survival rate at four years is still identical (83%) for

the three newly approved drugs as well as other novel therapies into clinical practice:

- For initial therapy, choose between a combination of bortezomib, lenalidomide, and dexamethasone or bortezomib, thalidomide, and dexamethasone (if lenalidomide is not available). For frail patients lenalidomide-dexamethasone is also a potential “simple regimen with an outstanding side-effects profile.” And he said that even though ixazomib was approved in previously treated patients, he believes the combination of ixazomib, lenalidomide, and dexamethasone may be useful for some newly diagnosed patients, including those who cannot take bortezomib because they have no access to it, are too frail, or who develop peripheral neuropathy on bortezomib.

- For high-risk patients, he suggested a combination of carfilzomib plus lenalidomide-dexamethasone or bortezomib-lenalidomide-dexamethasone plus elotuzumab or daratumumab. The monoclonal antibodies are now being tested in these combinations in clinical trials, he said.

- As for maintenance, he said that in the future he expects researchers to determine the optimal duration of lenalidomide maintenance. He suggested using lenalidomide maintenance for standard-risk disease and bortezomib for high-risk disease. “New drugs may play a role in maintenance in those with high-risk disease or for those who find it difficult to receive an injection every two weeks.” Ixazomib might be an alternative maintenance drug, with monoclonal antibodies added in for high-risk disease patients. He warned that daratumumab should not be taken into frontline

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Learning Objectives for This Month’s CME Activity: After participating in this CME activity, readers should be better able to incorporate into community practice three new drugs for the treatment of myeloma.

both early and late transplant recipients. He suggested offering late transplantation to standard-risk patients who tolerate therapy well, along with those who prefer to delay going to transplant.

## Initial, High-Risk, and Maintenance

Rajkumar suggested the following specifics for oncologists to incorporate

## CME Article

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therapy yet: “Don’t jump the gun. We need to see whether we get therapeutic benefit with these drugs at early stages.”

## Relapse/Refractory

**Paul G. Richardson, MD**, Clinical Program Leader and Director of Clinical Research of the Jerome Lipper Multiple Myeloma Center at Dana-Farber Cancer Institute and Professor of Medicine at Harvard Medical School said that treatment options for patients with relapsed or refractory disease are more challenging: “The degree of proteins evaluated to see the extent of disease may not reflect the underlying disease burden. For patients who relapse on maintenance, the time to next therapy may be longer. It is important to consider the response to prior therapy in the relapsed setting,” he said, noting that clinicians can revisit drugs that have been previously used.

“We have three extraordinary new agents to save patients. Elotuzumab and ixazomib are important advances in relapse. Patients live longer and with better quality of life. The three new approvals add profoundly to our armamentarium.”

Older patients need to be treated more gingerly in the community, Richardson added. Pre-existing peripheral neuropathy, renal impairment, and cytogenetic problems can change over time. In the relapse setting, the aggressiveness of the disease, including the number of relapses, and refractoriness to treatments is important.

## ‘Clonal Heterogeneity is Real’

“Clonal heterogeneity is real. We need to throw a big net over the disease,” he said.

He argued that clinical trials of early relapse with the newer drugs are vital. “If the new drugs fail in clinical trials, we can still use other novel therapies.”

Patients with advanced multiple myeloma have a poor prognosis, and “the advent of these new drugs gives us a chance to affect this challenging group of patients.”

Richardson outlined rational combination strategies for patients with relapsed/refractory multiple myeloma: “Use an IMiD or bortezomib as a baseline and then add in other drugs. Triplet therapy is emerging as the new standard of care,” he said.

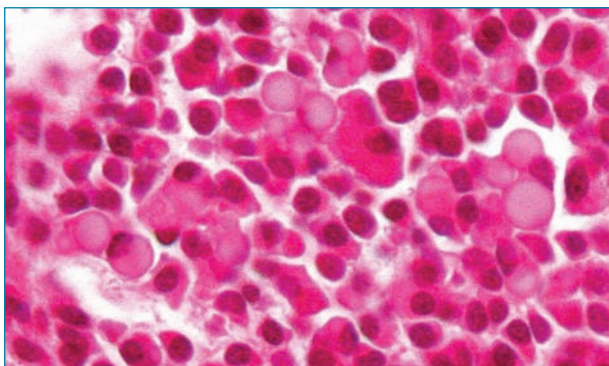
The second-generation proteasome inhibitor carfilzomib is “an important agent to integrate into relapsed/refractory therapy,” he said.

“The combination of carfilzomib plus lenalidomide-dexamethasone is most promising and is well tolerated, with none of the neurotoxicity or challenging side effects of other proteasome inhibitors.” He noted that clinicians need to balance toxicity with drug benefits when selecting therapy.

“Ixazomib is a remarkably well-tolerated agent taken once a week and is very useful in older, high-risk myeloma patients, and there appears to be no difference in three-drug versus two-drug regimens including ixazomib.

## TOURMALINE-MM1 Study

Richardson pointed out that the results of the Phase III TOURMALINE-MM1 study presented at the ASH meeting (*Moreau, Abstract 727*) showed that the combination of ixazomib plus lenalidomide-dexamethasone led to a 35 percent improvement in PFS over lenalidomide-dexamethasone without a substantial increase in overall toxicity, including cardiac toxicity and peripheral neuropathy.



A combination of pomalidomide plus lenalidomide and dexamethasone is another “provocative partner” with any of the three new drugs, he continued. Also, combinations of the histone deacetylase (HDAC) inhibitor panobinostat and ixazomib are moving

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forward in clinical trials. The upregulation of CD38 by HDAC inhibitors makes them ideal partners with daratumumab, he said.

Trial results are also encouraging for improved outcomes with the combination of pomalidomide and dexamethasone plus daratumumab.

## ELOQUENT Trial

The ELOQUENT trial showed that a combination of elotuzumab plus

bortezomib yields a progression-free survival benefit, and data are emerging from combinations of elotuzumab with proteasome inhibitors, as well as elotuzumab and ixazomib with other immunomodulatory drugs (IMiDs).

The integration of novel agents has made an impact on patients with relapsed/refractory multiple myeloma, he said. “Innovations to date such as proteasome inhibitors and IMiDs have produced significant improvements in progression-free and overall survival. The recent approvals will augment this.

“The next wave of therapies is driven by mutations and plasma-cell biology, such as daratumumab and elotuzumab—two first-in-class monoclonal antibodies, and they have led to a paradigm shift.”

Baseline immune function also appears to be a key barrier to success, but may be targetable with the use of programmed death 1 and programmed death ligand 1 blockade.

“Monoclonal antibodies have activity in high-risk disease and represent a true,

new novel mechanism. Other novel immunotherapies include checkpoint inhibitors and vaccines,” Richardson said. “New insights into the mechanisms of drug action—for example Panobinostat—are further expanding therapeutic opportunities with combinations.” Numerous other small molecule inhibitors show promise as well.

“Outcomes in multiple myeloma continue to progress and provide real hope. I applaud the FDA for its remarkable effort over the last year,” Richardson said.

## Q&A

The panelists were asked whether it was possible to tease out important nuances in combinations of elotuzumab, carfilzomib, or ixazomib to help community oncologists make treatment decisions. Rajkumar agreed that it will be important to find biomarkers for better responses.

Another audience member asked about the role of cytotoxic therapy. “Cytotoxic therapy should not be forgotten,” Richardson said. “We can revisit their biochemistry to derive newer, less toxic agents. Also, patients who return to cytotoxic therapy after immunotherapy may revive a response.”

Rajkumar added that myeloma patients usually have to move on to succeeding regimens. “Cytotoxics are good drugs. We need all therapies,” he said, noting that the combination of cyclophosphamide, bortezomib, and dexamethasone is an extremely well-tolerated regimen.

A long-term myeloma patient commended the panelists and agreed it was appropriate to celebrate the three new drug approvals: “Now get back to work,” he said. “The war is not over.”

In closing, the FDA’s Deisseroth said: “It has been an inspiring year personally. I’m grateful for the opportunity to participate in the process.”