# Advances in Multiple Myeloma

**Dates of Certification:** *August 21, 2015, to August 21, 2016*
**Medium:** *Print with online posttest, evaluation, and request for credit*


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***Disclosure:*** *Grant/research support: Genentech/Roche, Pfizer, Puma Inc, Novartis (clinical trial support contracted to the University of Southern California and MD Anderson Cancer Center); consultant: Eisai, OncoPlex Diagnostics, Merck, Novartis.*

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**Overview**
*This activity is designed to inform physicians about the latest treatment advances and data in the field of multiple myeloma, including both recently approved and investigational treatment strategies.*

**Target Audience**
*This activity is directed toward hematologists and medical oncologists who manage and treat patients with multiple myeloma. Transplantation specialists, radiation oncologists, pathologists, fellows, nurses, nurse practitioners, physician assistants, and other healthcare providers interested in the treatment of multiple myeloma are also invited to participate.*

**Learning Objectives**
After participating in this CME activity, learners should be better prepared to:
- List recently approved treatments for multiple myeloma by class of agent
- Summarize findings of elotuzumab from ELOQUENT-2
- Describe outcomes data of carfilzomib from ENDEAVOR and ASPIRE
- Identify the rationale for combining HDAC and proteasome inhibitors for the treatment of multiple myeloma

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Although multiple myeloma remains a largely incurable malignancy to date, advances in treatment options have succeeded in prolonging patients' survival times. A little more than 15 years ago, the average patient with newly diagnosed myeloma was about one-third as likely as someone without the disease to live another 5 years. By 2009, that number had risen from one-third to about 45%.[1] In the 1990s, growing use of stem cell transplantation was the cause of some of the improvements in survival rates, which was followed by continued improvements in the 2000s with the introduction of the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide and the proteasome inhibitor (PI) bortezomib.[1,2]

When the disease almost inevitably relapses after treatment, it returns in a form that is typically refractory to the currently available treatment options.[3] There is obviously still room for improvement, whether that means prolonging survival, decreasing toxicities, overcoming mechanisms of resistance, or simply providing a more convenient administration method for patients. One of the novel strategies under investigation involves the use of monoclonal antibodies (mAbs), which have been used successfully in many other cancers in the past few years, but until now have had limited success in treating multiple myeloma.[4] Two of the mAbs being studied in this field are elotuzumab and daratumumab, both of which have received breakthrough therapy designation from the US Food and Drug Administration (FDA),[5] and both of which have demonstrated efficacy in clinical trials in multiple myeloma—elotuzumab in combination with lenalidomide and dexamethasone,[6] and daratumumab as a single agent.[7]

While the approval of the PI bortezomib undoubtedly represented a major breakthrough in the treatment of multiple myeloma, many mechanisms for inherent or acquired resistance to this treatment exist, limiting its long-term usefulness.[8] One novel strategy for overcoming some of the resistance to proteasome inhibition involves combining it with a histone deacetylase (HDAC) inhibitor, such as the recently approved panobinostat, which targets one of the possible resistance pathways.[9]

Newer PIs also are entering the therapeutic arena within the myeloma field, including carfilzomib, which was approved in 2012,[10] and ixazomib, which is still under investigation. Approved as a single-agent therapy that demonstrated durable antimyeloma activity with manageable toxicities,[11] carfilzomib is going through further investigation regarding combination regimens and earlier lines of therapy.[12,13] Meanwhile, ixazomib is still in phase III trials, but its pending approval as the first PI utilizing the oral route of administration is eagerly awaited.[14]

Perhaps the most revolutionary therapy being investigated is chimeric antigen receptor T-cell (CAR-T) therapy. In this approach, immune cells from a patient are extracted and re-engineered to express recombinant proteins (in this case, antigen-specific CARs), and then the re-engineered cells are reinfused into the patient. Complete remission (CR) rates of around 90% have been elicited using CAR-T therapy in relapsed/refractory pediatric acute lymphoblastic leukemia,[15] and researchers hope to replicate these results in the multiple myeloma setting.

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*Data on these current and emerging myeloma treatments were recently presented at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting. Ola Landgren, MD, PhD, chief of the Myeloma Service at Memorial Sloan Kettering Cancer Center (MSKCC) in New York City, shares his thoughts here on the key myeloma-related data, along with his perspective regarding where myeloma treatment might be headed in the near future.*

***Moderator:*** Dr Landgren, how do you think the phase III ELOQUENT-2 trial results fit within the context of unmet clinical needs in the relapsed/refractory setting of multiple myeloma?

**Dr Landgren:** The ELOQUENT-2 study presented at the ASCO meeting is the first phase III trial in myeloma using the mAb elotuzumab that targets the antigen signaling lymphocytic activation molecule F7, or SLAMF7. This antigen is expressed on the surface of myeloma and other cells. ELOQUENT-2 showed that patients treated with this drug in combination with lenalidomide plus dexamethasone had significantly improved progression-free survival (PFS) compared with patients who were treated with only lenalidomide plus dexamethasone.

Looking in more detail at this trial, the median follow-up was 24 months, and, when you review the difference in the median PFS between the 2 arms—19.4 months (95% CI, 16.6-22.2 months) for the elotuzumab/lenalidomide/dexamethasone arm compared with 14.9 months (95% CI, 12.1-17.2 months) for the lenalidomide/dexamethasone arm (hazard ratio [HR], 0.70; 95% CI, 0.57-0.85; $P$ = .0004)—you see that the difference was not only statistically significant, but clinically meaningful, as well. What this means is that patients who are treated with this drug combination would, on average, have a 4 and one-half month longer disease-free benefit compared with the control arm, which I think is very important to patients. There was also a difference in terms of the confidence intervals: in the elotuzumab arm, the 95% CI was between 16.6 and 22.2 months, whereas the interval in the comparator arm went all the way down to 12.1 and up to 17.2 months. In addition, the hazard ratio was 0.70, which means that patients have a 30% lower risk of progressing with the elotuzumab-containing regimen.

With several new treatment options coming into the field of myeloma, it is getting a little bit more crowded. When that happens, aspects beyond efficacy start coming into play, including safety and quality of life. Based on this trial and also on my own experience, I think elotuzumab is a very tolerable drug, both from the short-term and the long-term perspectives. It is an infusional therapy that is giv-

en on days 1, 8, 15, and 22 of a 4-week schedule for the first 2 cycles, and then it is given on days 1 and 15 of the subsequent cycles. Weekly infusions for 2 months, of course, are a little bit inconvenient. But once the dosing has moved beyond those initial 2 cycles, it can be dosed every other week. Combined with 4 and one-half months' benefit, in my opinion, it marks quite an important contribution to myeloma therapy.

***Moderator:*** What are the next steps for elotuzumab in terms of ongoing studies in frontline combinations with other available therapies, as well as in other settings in multiple myeloma?

**Dr Landgren:** I think it's a little bit too early to draw conclusions from ongoing studies of elotuzumab in other settings. We always have to wait for the data to come out, but from what it looks like, I think the results seem to be quite consistent. The drug seems to continue to deliver, and the data have shown that it is not a very toxic drug. It's quite tolerable. So I think it's an important drug. Given the fact that there is no established curative therapy for multiple myeloma, we need a lot of options, and this is a good one.

***Moderator:*** Can you tell us about the phase II trial data released at the ASCO meeting about the anti-CD38 mAb daratumumab and the potential clinical implications?

**Dr Landgren:** Daratumumab is 1 of 3 CD38 mAbs, along with SAR650984 and MOR202. These 3 drugs all target the CD38 antigen, which is highly expressed on the surface of plasma cells. As with elotuzumab, daratumumab seems to be efficacious and safe, and quality of life is good.

One thing that differs between the CD38 antibodies and elotuzumab is that the CD38 antibodies have demonstrated efficacy as single drugs. Elotuzumab was also explored as a single drug, but it did not deliver; however, it showed an additive effect, as just discussed, when used in combination with lenalidomide and dexamethasone. Both daratumumab and SAR650984 have already been found to deliver as single agents (in terms of durable responses).

Ongoing trials are exploring these molecules in combination with a range of different drugs. The data are not fully mature, so it is too early to know definitively how they will fare, but what we have seen so far is that they seem to be very tolerable. In 6 to 12 months, we will have a lot of exciting data to review, and we will see which are the preferred combinations. They are currently being tested in combination with PIs, IMiDs, and steroids. Some studies also use a CD38 antibody instead of steroids. So I think the upcoming 6 to 12 months are going to be extremely interesting when it comes to mAb data in myeloma.

If I were to speculate based on the existing data, I think it is very likely that we are going to end up with a combination regimen of up to 4 drugs for the treatment of myeloma. Such a combination could include a PI, an IMiD, low-dose steroids—maybe lower than we currently use—and mAbs. Because many of these drugs are individually new and expensive, combining them will create a huge problem in terms of their extreme cost. The cost effectiveness has to be considered as well, though. If 4 drugs are given simultaneously—let's say carfilzomib, daratumumab, lenalidomide, and dexamethasone, as an example—for 10 cycles that potentially cured patients' myeloma, although the combination would be expensive, it would still be a more attractive option than using a 3-drug combination over and over again. We are not yet sure whether less-aggressive therapy can result in a greater expense in the long run. This issue will need to be worked out. But, from an efficacy perspective and also from a quality-of-life perspective, I think this potential combination is very attractive, both for newly diagnosed myeloma as well as in the relapsed setting.

***Moderator:*** Are there any studies currently under way of daratumumab in the setting of smoldering myeloma?

**Dr Landgren:** Yes. There is a newly opened, multicenter study that my institution is participating in to investigate dosing schedules of daratumumab in patients with smoldering myeloma. It makes sense to use mAbs in patients who are not immunocompromised because you are taking advantage of the patient's own immune system. We know that multiple myeloma itself is usually associated with immunosuppression. Many of the myeloma drugs studied to date cause a lot of immunosuppressive complications. So, using mAbs for patients with early disease is a very logical approach, and studies of this approach are ongoing.

***Moderator:*** Can you tell us about what was learned at the ASCO meeting about carfilzomib from the ENDEAVOR trial that evaluated carfilzomib/dexamethasone versus bortezomib/dexamethasone in patients with relapsed multiple myeloma?

**Dr Landgren:** It is a very interesting era we are in right now in terms of myeloma research. There are the new drugs we just talked about, the CD38 and SLAMF7 antibodies. Also, there are drugs that I still consider to be new, despite gaining FDA approval about 2 years ago, such as carfilzomib, which we are learning more about now. Interim results of the ENDEAVOR study showed that depth of response, duration of response, and PFS were improved in the carfilzomib/dexamethasone group compared with the control group, which was treated with bortezomib/dexamethasone. So, carfilzomib helped to achieve deeper, longer responses.

Multiple studies in the past 6 months support the favorable findings from ENDEAVOR. A study published in *The New England Journal of Medicine,* called ASPIRE, investigated the combination of carfilzomib/lenalidomide/dexamethasone versus lenalidomide/dexamethasone in relapsed multiple myeloma. In the ASPIRE trial, PFS was 26.3 months in the carfilzomib group versus 17.6 months in the control group, which is essentially a 9-month difference in benefit. That is a pretty long time. Also, to put these results in context, 26.3 months was in patients with relapsed disease; this is longer than the median PFS achieved by many agents in patients with newly diagnosed disease.

Also, very recently, a National Institutes of Health (NIH) study was published. It investigated carfilzomib/lenalidomide/dexamethasone for both newly diagnosed and high-risk smoldering myeloma,

showing that all 12 of the patients with smoldering myeloma and 28 (62.2%) of the 45 patients with newly diagnosed myeloma achieved at least a near CR. None of those patients had received a transplant, and nearly all of them reached the point of minimal residual disease (MRD) negativity. So, here we have seen multiple studies showing that carfilzomib really delivers.

I think a key aspect with carfilzomib that is also being determined now will be the optimization of the dosing to make it a bit more convenient. Ongoing studies right now are exploring whether it can be given once a week instead of twice a week by increasing the dosage. Hopefully, those results will be available in the next few months. That will make that drug even more accessible for patients.

***Moderator:*** Are there any signals that increasing the dosage of carfilzomib could increase the risk of neuropathy?

**Dr Landgren:** That's a very good question. None of the trials we have been discussing—ENDEAVOR, ASPIRE, the NIH studies—have found any grade 3 or higher peripheral neuropathy. They also have not encountered any worsening of peripheral neuropathy. If anything, there has been discussion of a possible cardiovascular signal. However, the largest study of them all, with 792 patients, was the ASPIRE trial, and that study found no significant difference in terms of cardiovascular outcomes between the 2 treatment arms. For now, that is the strongest evidence we have. What you could argue against is that the dosing for carfilzomib in ASPIRE was 27 mg/m$^2$ twice a week, and some of these new trials are now considering using higher dosages. The full story is still unfolding, so we will have to wait for the ongoing work to fill in the blanks.

***Moderator:*** Can you elaborate on the issue of eliminating MRD in the context of some of the more potentially potent combinations that are currently being evaluated in clinical trials?

**Dr Landgren:** Across the board, a lot of studies are currently looking into the role of MRD testing in multiple myeloma. I recently searched on clinicaltrials.gov and found 34 myeloma trials that include MRD testing. I also did the same search on PubMed and found 424 publications in myeloma. This is an exploding field. Also, I worked on a recently published review paper in *Nature Reviews Clinical Oncology* with Sham Mailankody as the first author, which comprehensively reviews the role of MRD around the world. What we found is that no matter how MRD has been defined or measured—by flow cytometry, molecular sequencing, etc—MRD negativity is always associated with significantly more PFS and overall survival (OS) than MRD positivity. That is consistent.

The last thing I want to say along those lines is that there are now emerging data showing that the depth of MRD is associated with clinical outcome, both PFS and OS. So, if you are MRD-negative with a tool that is sensitive to $10^{-3}$ versus $10^{-3}$ to $10^{-5}$ or $10^{-5}$, there is a difference. A very recent paper published in *Blood* by the British investigators Rawstron et al from Leeds, England, suggests that for each log increase in MRD negativity—meaning, for every 10-fold improvement—you gain 1 year of OS. So, if you can increase MRD negativity from 1% to 0.1% or from 0.1% to 0.01%, you gain another year.

Different drugs deliver different depths of response and MRD negativity. This concept is being explored in several different drug combinations. Even trials with drugs that have been around for a long time are looking more carefully now at patients who are in CR. Some of these trials show a difference between some patients in CR in terms of their MRD status. And there is a difference in PFS and OS between these groups. I think the field is now using many new and effective drugs that are not very intense. And I expect that with the new MRD tools, we will be able to see deeper and deeper MRD negativity, which does translate into better outcomes.

The very last piece along these lines is that we held an international workshop on MRD testing in myeloma here at MSKCC on July 10, 2015. To me, it was striking to hear that, of the 70 experts in the room, everyone, even the flow cytometry experts, agreed that the molecular MRD tools are going to be the future because they are more sensitive, deliver better results, and soon are going to be more easily available. So that was very interesting.

***Moderator:*** What are the recent data concerning some other novel mechanistic approaches in earlier stages of development [eg, CAR-T therapy]?

**Dr Landgren:** CAR-T therapy is a relatively new concept in hematology. It has been studied in acute leukemia and lymphomas for a few years now. A few studies recently have been initiated for this therapeutic strategy in multiple myeloma. The first clinical trial that opened for myeloma was at the NIH with Jim Kochenderfer's group. He had performed preclinical work targeting B-cell maturation antigen (BCMA), which led him to extract T-cells out of the patient, re-engineer the cells genetically, and return the re-engineered T-cells to the patient's body. They look for BCMA that is expressed on the tumor cells; if they are there, the procedure can be performed. So far, this technology is in phase I, so no efficacy information is currently available. The dosage is being defined, and safety is being explored.

The second study of CAR-T therapy for myeloma was developed by Carl June at the University of Pennsylvania. His group developed CAR-T therapy a few years ago for lymphoma. Lymphomas express CD19, a B-cell marker. So, Carl June hypothesized that maybe B cells are more important in myeloma than previously thought. Although myeloma is considered to be a plasma cell disease, there is some evidence that other cells could play a key role. As recently presented, they gave CD19 CAR-modified T-cells to 6 patients with myeloma. The best result was achieved by a patient who had previously been treated with an autologous stem cell transplant (ASCT), and later received a second ASCT with CAR-modified T-cells. The duration of the effect was longer this time than it was the previous time, which was considered to be a striking finding, because typically, each successive ASCT lasts a shorter amount of time than the previous transplant. On the other hand, another patient in this trial received a transplant and the T-cells, but this patient's disease progressed. It is

too early to make final conclusions based on the short follow-up and the small numbers involved in this study, with 1 patient who seemed to have a good effect and other patients whose disease progressed.

B-cell maturation antigen is a myeloma target, whereas the University of Pennsylvania uses a CD19 target. We do not yet fully understand the implications of these 2 targets. Other groups, such as those here at MSKCC, are also working to develop CAR-modified T-cells. Although you use the cells, what this strategy is attempting to do is to target antigens on the surface of either tumor cells or other cells, which is the same strategy as that of the mAbs and other treatments. There are so many different ways to try to manipulate the immune system, such as with vaccines, viral therapy, or even some small molecules. So, although we think of these as very unique strategies, they are simply different tools to try to kind of take advantage of these mechanisms. However, these mechanisms can sometimes be approached by other strategies.

***Moderator:*** Can you tell us a few things that have happened recently with panobinostat and the oral PI ixazomib?

**Dr Landgren:** The HDAC inhibitor panobinostat was approved earlier this year. The reason this class of medication was explored in the context of multiple myeloma in the first place was because, mechanistically, discovery work had shown that if you block a proteasome, you have to cross all cells in the body. Myeloma cells, in particular, are very, very susceptible and will die with this strategy. Blocking the activity of proteasomes, which degrade misfolded proteins, causes accumulation of misfolded proteins in the cell, which becomes cytotoxic. That is the mechanism that is believed to kill myeloma cells. Myeloma cells are smart, though, and, over time, they find a way to get around the problem we caused for them by blocking the proteasome. Ubiquinated proteins work together with HDAC6, which is a specific subclass of HDAC, causing the proteins to form aggresomes, which are proteins that have been assembled in a specific way. They are then sent to lysosomes, which take the proteins apart. So, if the proteasome is blocked, cells can still use other mechanisms to bypass the problem, such as by using lysosomes to do the job instead. In this way, the cell avoids the proteasome killing effect. And, since HDAC6 is responsible for the escape mechanism, there seemed to be a rationale to attempt to inhibit both HDAC6 and a proteasome simultaneously.

Vorinostat, which is a pan-HDAC inhibitor, was the initial drug developed in this class. While the benefit it produced was statistically significant, it was a difference of only a few weeks. Therefore, it was not approved. Panobinostat was then developed for myeloma, and did gain approval earlier in the year based on its significant 4.8-month benefit, which was deemed to be clinically meaningful. Panobinostat was given in combination with bortezomib plus dexamethasone versus bortezomib plus dexamethasone on the control arm. Although the combination of the HDAC inhibitor and the PI produced a significant and clinically meaningful difference, many patients experienced grade 3 diarrhea. There were also other safety signals, such as bone marrow toxicity.

After the drug was approved, we have learned over the past few months that maybe panobinostat can be combined with other drugs, for example, carfilzomib. Although the rationale for using it with a PI was there, as I just explained, data also exist to suggest that an IMiD may be an option due to the redundancy in the mechanism of action between the PIs and IMiDs. We do not fully understand how these drugs work. The recently presented data suggest a much better toxicity profile, with far less diarrhea, even with increasing dosages of panobinostat. Using a low dosage in combination with these other drugs may be the way to go. This is another example of a drug that is already approved, and yet we are still learning the best ways to use it. Panobinostat will probably be a drug that is used mostly for patients who have already tried many other options that did not work, until further data can answer these questions to allow it to be used in a broader context.

The oral PI ixazomib also is currently being investigated in clinical trials. Ongoing phase III trials are comparing ixazomib/lenalidomide/dexamethasone with lenalidomide/dexamethasone in the control group. Earlier this year, the manufacturer of ixazomib issued a press release to indicate that at the study's first prespecified interim analysis, the drug was found to add significant benefit in terms of PFS compared with the control arm. No detailed information was communicated at any of the recent conferences, but perhaps we will hear more about it at the upcoming 2015 American Society of Hematology (ASH) Annual Meeting. At a prior ASH annual meeting, phase II trial data were presented showing that maintenance treatment with single-agent ixazomib deepened the responses achieved by lenalidomide/dexamethasone induction therapy, and that it is tolerable. This represents an opportunity to use an established target, the 20S proteasome, in an oral fashion with once-weekly dosing, which would be a very attractive option.

My take on all of this is that the deepest responses seem to come from the intravenous PI carfilzomib. Data from the ENDEAVOR and NIH trials seem to indicate that it can be a very attractive option for younger patients as combination therapy, producing very deep, durable, MRD-negative responses. We do not yet have head-to-head comparison data for the ixazomib/lenalidomide/dexamethasone combination regimen, but it does seem to be a very powerful combination that could be extremely attractive for older people or for younger patients for whom convenience or preference side against intravenous administration. I think the new baseline therapy will include 3 drugs, and, unless there is a reason not to use a triplet combination, I think most patients in the next 6 to 12 months could receive such a regimen, which could include a PI, an IMiD, and a steroid. We have even touched upon adding a mAb to that for some patients. The field has left 2-drug regimens behind now in favor of upcoming 3-drug options, which could turn into 4, which will create issues to resolve regarding cost.

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