MULTIPLE MYELOMA

SANDRA E. KURTIN, RN, MS AOCN, ANP-C Our next session is on New Drugs and Novel Mechanisms of Action in Treating Patients with Multiple Myeloma. Pleased to have here with us today, Ms. Charise Gleason and Dr. Jonathan Kaufman, both of the Emory University School of Medicine and Winship Cancer Institute.

CHARISE Jonathan and I work together in our myeloma program at Emory, and we're going to do this talk like how we work: back and forth. It's very much a collaborative relationship. The advanced practice providers in the myeloma program are very involved in the clinical trials and pretty much every part of what we do.

We're going to talk to you about new drugs. These are the learning objectives; talking about different mechanisms of action. We're going to talk a little bit about some old drugs too, toxicities, how we monitor early signs of toxicities that providers need to be aware of, especially with these newer agents, and some of the newer optimal regimens, how we make our decisions about how we treat these patients.

Our financial disclosures.

DR. KAUFMAN: When we think about plasma cell disorders the first time when we see a plasma cell disorder, we make the decision about how to classify that, how to divide it. The first thing that we do is we look at the percentage of plasma cells. What the percentage of plasma cells does is it allows us to distinguish between MGUS, where there's less than 10% plasma cells, and

the M-spike is less than 3 gm/dL, and myeloma, when you have more than 10% plasma cells or more than 3 gm of a paraprotein.

Then once we make the diagnosis of myeloma, we then further subdivide into whether that's symptomatic or asymptomatic. Symptomatic myeloma is defined as broadly one of two things; they either have to have symptoms and we use the acronym CRAB for the CRAB criteria, hypercalcemia, renal dysfunction, anemia, or lytic bone disease, or you have what we have now described as "myeloma-defining events." The myeloma-defining events are those bottom three on the symptomatic myeloma chart; that is, if the bone marrow biopsy shows greater than 60% plasma cells or the serum free light chain involved over uninvolved, the ratio is greater than 100, or there's greater than one focal lesion on the MRI.

Those three are new to the diagnostic criteria for symptomatic myeloma or a myeloma that requires treatment. We used to treat these patients as smoldering myeloma, but we found if a smoldering myeloma had one of those three, then 90% of those patients had symptoms in the next 6 months to 1 year and, hence, we said, "We should just initiate therapy early."

It looks like there'll be about 30,000 new cases of myeloma, still with 12,000, 13,000 deaths. Despite the fact that we consider myeloma a very treatable disease and every once in a while we have a patient who will get treatment and never relapse, in large part, we don't consider this a curable disease. It is a disease that typically patients present in their late 60s, earlier 70s, but you can see myeloma in younger patients.

We don't know why patients get myeloma. And then in survival going back 20 years, 20 or 30 years, median survival was on the order of 2 to 2.5 years. If you look at probably 10-year-old data at this time, median survival was probably 5 years. If you look at the trends and data, my presumption is when we look back at patients diagnosed in 2016, median survival will likely be on the order of at least 6 to 8 years.

From a historical perspective, the first documented cases were over 150 years ago. And then the real beginning of improvement and outcomes of myeloma came with the development of high-dose therapy and transplant in the mid-90s. Then, as with the rest of oncology, in the late 90s/earlier 2000s, we started to see new drugs. We saw drugs like thalidomide, lenalidomide, and bortezomib change outcomes, and we've had improvement of those drugs with drugs like pomalidomide and carfilzomib. Then just in the past year alone, we've had four new drugs approved: panobinostat, elotuzumab, daratumumab, and ixazomib, and we'll spend a fair amount of time today talking about those new drugs.

From a smoldering myeloma standpoint -- again, in smoldering myeloma the risk of progression to myeloma is about 10% per year. And the reason we don't treat all of these patients is that even though it's about 10% per year, after the first 5 years that percentage, that risk, decreases significantly. So there are still some patients who if you look pathologically, for all the world looked like they have myeloma, but they don't have any symptoms. And people can go without symptoms for a very long time.

No prior therapy has shown to be beneficial. There was a single study done in Spain, which looked at lenalidomide plus dexamethasone versus observation, and in that relatively small study there was suggestion of a benefit. The study had such problems with design and execution that we in the United States have not incorporated that into our practice. In large part, we're waiting on an almost completely accrued ECOG study that looks at lenalidomide versus observation in smoldering myeloma patients, and preliminary data shows that that's a safe approach and we're just waiting for the final day to show that's effective.

Not to look at any of these individually, but this shows you that there are many studies here in the United States asking the question, "Can we treat patients earlier and impact long-term outcomes?" And here's the list of studies that are currently open asking that question.

I talked to you about the indications for treatment, the CRAB criteria, and the myeloma-defining events. And I'm going to turn it over to Charise. And one final comment. We have a new staging system that not only includes the old ISS staging system using beta-2 microglobulin, as well as albumin, but now we're looking at underlying biology. That is, the underlying high-risk FISH features, like 17p, 414, or 1416, as well as markers of the proliferative index like an LDH. And then we can restratify using all of these things together into what we call a standard risk and then high risk, and those help us make decisions in a large part the way we practice. It doesn't help us make our induction decision; what it helps

us make decisions is how to manage the patient after they've achieved remission.

And now I will hand it over to Charise.

CHARISE You think when a patient comes to us the first thing that we want to think about for induction therapy are are they a transplant candidate or not? It's going to drive our decision in how we treat them because a nontransplant candidate you do not want to have an alkylating agent.

Right now, these are the FDA-approved drugs. You've seen that; there's a long list for a somewhat rare disease. This is the NCCN guidelines. It's interesting; I had a student with me 2 weeks ago who didn't know anything about myeloma, but she's used to looking at those NCCN guidelines and said, "How do you know how to treat?" And that's a good question and that's what we do and that's what the data tells us, and so that's what we're going to walk through. To put it in perspective, we're going to present a case throughout the rest of the talk.

We had a 65-year-old gentleman who presented with anemia, bone pain, and you can see on his initial workup, he is a bit anemic. His white count and platelets are fine; his protein is 9.9; skeletal survey showed extensive lytic disease; his SPEP and UPEP; he's got an IgG paraprotein and a urine paraprotein; his bone marrow was about 50% and no high-risk features. How do we decide how we're going to treat this patient?

We always want to think about a clinical trial. Not everybody wants to do that, but for our patient, we want to go back and look, what is the backbone of our treatment for induction therapy? Because like Jonathan said, we're going to

look at those risk factors. But what drives that up-front treatment is pretty standard unless your patient presents with plasma cell leukemia.

The backbone of an induction therapy has been lenalidomide and bortezomib with dexamethasone. And there's been a discussion for some time in the myeloma world, "Do we give two drugs or do we give three drugs?" I can tell you at our center, we've been giving three drugs for some time. And at ASH last year, data from SWOG was presented where they looked at a randomized phase III trial looking at bortezomib, lenalidomide, and dexamethasone versus that standard of care lenalidomide and dexamethasone. You can see that the three-drug regimen was superior.

You do have a few more adverse events, but that's why you have to monitor and watch these patients closely. There's neurologic changes because now you've added bortezomib in there, some pain, GI symptoms; but those are the things you're going to monitor with almost every therapy we put on these patients.

Another trial is the IFM trial; this is the French group, along with the United States, the Dana-Farber. This is the phase III trial and this data is from the French trial. We're still enrolling in the United States on our portion. So, it looked at RVD again; all patients got three cycles of induction, went on to a cyclophosphamide stem cell collection, and were randomized to either early or late transplant; everybody continued on therapy. We don't have the data from our portion of the trial and we're still enrolling, but already data is showing us that that transplant piece is superior.

If you've been dealing with myeloma for a while, you know that the trend goes back and forth; transplant's been a mainstay of myeloma for some time. Ten years ago we started cherry-picking a little bit, maybe delay some of these transplants, but the data is telling is and pointing to transplant up front is better for our patients. Certainly a patient with high-risk features wouldn't want to delay moving on to transplant.

The other piece to remember with the French trial is that their maintenance arm stopped. In the United States, we have access to these drugs, we continue on maintenance, and our trial continues on maintenance, as well in the United States, so that data is a little different. So it'll be interesting to see what the data looks like when we have it from the U.S.

Also of note, a European trial, anybody older than 65 would not be considered for transplant, so if you work at a transplant center, in the United States, 70s -- there's probably somebody out there who's transplanted an 80 year old -- but we look more at that performance status and they have that 65 cutoff.

When we look at our patient -- he didn't want to do a clinical trial -- so he did go on to do RVD. He was an ISS stage 1, he didn't have any associated high-risk features with his disease; he got stem cells collected after four cycles, went on to transplant. At day 100, he was in complete remission and was placed on lenalidomide maintenance. And I'm sorry, in your slides that transplant is missing on yours.

At our center we're very aggressive with maintenance, and I don't know if Jonathan wants to add to that, but even a patient in complete remission, we're going to offer them maintenance on that. The median time to progression after a transplant without maintenance is 2 to 3 years; with maintenance, 4 years and on and on like that.

This patient did well for 4 years, starts to develop asymptomatic biochemical relapse. So you have to think about that, when these patients start to progress, we don't necessarily immediately want to start treating them. It's a little bit difficult for a patient; we go back to that stage before they had symptoms and look at that. We want to watch a biochemical relapse very carefully, we don't want to wait until they have symptoms and come in with a fracture. But they might be an IgG myeloma who starts to have a free light rise; you're going to watch that carefully. You might decide to get a marrow just to recheck disease status or a PET to make sure you're not missing something, a surprise on the disease, because as we know with myeloma, disease can change.

This patient, again, did well for 4 years, biochemical relapse over a period of time -- about for 12 months -- and now has a protein again of 1.2, some anemia, so we're starting to see symptoms and it's time to treat. What do we do with this patient at this point? Because you looked at those NCCN guidelines, it's all over, right?

A few definitions as we move on; relapse myeloma, this is a previously treated patient who, after a period of being off therapy, requires salvage treatment. Your refractory patients; disease that is nonresponsive while on

therapy or progresses within 60 days of the last therapy. Then we have that relapse/refractory; these are your patients who never had much of a response, they didn't even achieve a minor response or better, and they become unresponsive while on salvage therapy or within 60 days of their last treatment.

This is something you're probably familiar with, this is the pattern of myeloma patients. We have different variations of this, but it's a period of asymptomatic, active, and then relapse. You can look and see again your patient as we start front-line treatment, they tend to have a longer response for a while, but as they start going out in that relapse when they're starting to be more exposed to multiple therapies, less response, less duration, and by the time we get to refractory, at that point our goal of therapy is very different than we were up front. Up front, we want to drive these people into remission, no minimal residual disease -- you hear a lot about MRD testing. But in that refractory, you know, your goals change. You want to get stabilization of disease and not have further damage.

When we're thinking about how do we treat these patients, first and foremost you want to remember there's a person sitting in front of you. In myeloma we get very caught up in numbers and charts and how you're responding, but we want to remember that patient. What was their last therapy? What kind of side effects do they have from those therapies? What are their other comorbidities? You want to think about those things. But when we're looking at the disease characteristics, we want to look at how deep was their response? How rapidly are they progressing? Is this somebody like our patient has a slow

biochemical relapse or is this person just rapidly progressing where you have to do something now? These are all things that we want to consider; always a clinical trial, and then you also want to think about could this patient be a candidate for another transplant?

Here's the scheme of what we look at with your relapse patients. A transplant patient, transplant eligible, if they relapse post-transplant within a year, you don't want to think about another transplant because we know they're only going to get half that response. Somebody who comes back to us who's 4 years out, you at least want to have that discussion. You know, we have all these new therapies, so we don't always go back to transplant like we used to. But we still have patients out there that are 5 and 6 years out, 7 years, that have done well, that haven't had any of these new agents, and you want to think about another transplant on them and then a different maintenance type program.

You can see, a patient who progresses in that first year, you're going to do something different. Your nontransplant patients -- again, you're looking at how quickly they relapsed on that last treatment. Somebody who had an induction and maybe a year later is progressing, you could consider that same therapy again.

These are a few of the newer agents that are approved in the relapse and refractory setting; two new proteasome inhibitors: carfilzomib and ixazomib. We have pomalidomide and an HDAC inhibitor, panobinostat, and we've already shown these a little bit. I'm going to run through a few of these drugs and then I'm going to be turning it back over to Jonathan.

Pomalidomide, a newer IMiD, a little more potent than lenalidomide was. We have yet a new IMiD right now that we're using on clinical trials coming your way soon. This is a 4 mg dose. The thing with this particular one, it is myelosuppressive, so you do have to watch patients' counts in a relapsed setting. Again, you're not going to be using this single agent, you're going to typically have it with something else, so you've got to watch those counts. You want them on something for DVT prophylaxis. Any IMiD, no matter what the dose, you want to prophylax for clots.

Fatigue, you know, it's a big problem in our world for everything and, you know, patients want that quick fix and then you have to tease out -- is it the drug? Is it depression? Is it pain? All those things. But fatigue can be a big problem with this drug as well. You can see those. We don't see a lot of neuropathy with pomalidomide; a little more constipation.

Carfilzomib, this is a new proteasome inhibitor; you had bortezomib, and now carfilzomib. It's a little more directed on its therapy, so we don't see the same neuropathy that we saw with bortezomib. It's IV. When we used it in the early clinical trials the 003/004, we hydrated the heck out of these patients and we started seeing all these pulmonary symptoms and cardiac symptoms and we were referring them to the specialist, and a lot of it had to do with the hydration. But there is a component; about 20, 25% of patients can have cardiac toxicity with this drug. So if you're putting a patient on this drug who has CHF, you really want to look at it, and do dose modifications, getting an echo.

We also know the first cycle of treatment with carfilzomib you can see a lot of shortness of breath anyhow, so you really need to monitor these patients closely. If it continues then you really want to assess them to make sure that you're not getting cardiac toxicity.

Fever is a little unique to this one and it's not when they're receiving it, it's when they go home, so making sure the patient knows. Again, some anemia. It's 2 consecutive days; 3 weeks on, 1 week off. I will tell you that in clinical trials we push the doses much higher. The starting dose for carfilzomib is 20 mg/m^2 and you escalate it up to 27. But on clinical trials, we're pushing it to 56 and 72 mg/m^2, and because you don't have that associated neuropathy. In practice, we go to weekly if a patient can tolerate it, so we do that pretty frequently.

This is the ASPIRE trial that helped get carfilzomib approved. It was a phase III that looked at standard of care lenalidomide and dexamethasone, so can we make it better if we add carfilzomib? Just like induction trials, the answer is yes. We did make it better; three drugs were better than two drugs.

This is the ENDEAVOR trial that compared carfilzomib and dexamethasone versus bortezomib and dexamethasone. Some of these patients had prior proteasome inhibitor exposure, and remember, these are relapse/refractory patients, and, again, the arm that had carfilzomib did better.

Ixazomib -- this on clinical trial was MLN9708; we've used it for years. This is an oral version of proteasome inhibitor. Patients now have an option to get an all oral regimen. It's also been used in the up-front setting on clinical trial, but it's approved in combination with lenalidomide and dexamethasone.

This is the trial, the TOURMALINE trial, that looked at standard of len/dex versus ixazomib, len/dex, and you can see the numbers. We had more CR rates, overall response rate a little better, but in general, the numbers were better and it could overcome some of those high-risk features that you saw in patients.

The dosing on this with ixazomib is they receive it once a week; 3 weeks on, 1 week off; starting dose is 4. Again, in clinical practice, I can tell you we do things a little different. Not everybody tolerates 4 mg. If they're in the post-transplant setting, we tend to dose at 3 mg and escalate up if they can tolerate it. They got weekly dexamethasone with this and lenalidomide was your standard dosing, 3 weeks on, 1 week off.

Some things about this -- you wanted to have your patient take it about the same time every day; 1 hour before food or 2 hours after; it shouldn't be taken with dexamethasone; antiviral prophylaxis always with any proteasome inhibitor. At our center, we put people on an antiviral and essentially leave them on it. Again, if it's in combination, which is how it's approved, with an IMiD, we do want to have the thromboprophylaxis in there.

DR. KAUFMAN Charise, you mentioned that you use it in different ways. While it's approved with lenalidomide and dexamethasone, any other ways of using it?

CHARISE We do. Do you want to talk about that?

DR. KAUFMAN I was just saying that while that was what led to the approval. We've used it with the same schedule and dose and possibly the maintenance setting after transplant, and we currently have a study, we've used

it in combination. We have used it in combination with other drugs, like we've used bortezomib or other proteasome inhibitors with other drugs, and found it to be safe and effective. There's emerging data, clinical trial data, to demonstrate that also.

CHARISE In our practice, in the maintenance setting, we'll use it on patients who are 414 positive because we know those patients are sensitive to a proteasome inhibitor. So when you're committing them to a maintenance route, now we have this oral option when we can get it approved, which is nice.

You can see the adverse reactions that occurred in 20% or greater. We have some GI things, some thrombocytopenia; it's that transient platelet drop that we saw with bortezomib -- no different on that -- 3 weeks on, 1 week off, some edema. You've got dexamethasone onboard, too, so you've got to take that into consideration.

Some patients when they're dosed on it the first time have some flu-like symptoms, and they'll call and it's like, "I took this pill and I have all this pain; everything hurts." Then they don't want to take it again. So you have to work them through it with the next dose, "Let's try to hang on there. Take a little Tylenol and try it again." Most people can tolerate it after they've gotten a few doses in. Then, again, we always have that option of dose-reducing to 3 mg.

DR. KAUFMAN The only final practice point about using ixazomib is that you have to remind your patient that they have three pills for an entire month and they take them the same day every week until it's over, so that's only three. On clinical trials when this message was not driven home, patients took this

medication on consecutive days, and that is extremely dangerous. Patients get very confused when they only have three pills for an entire month, so it's very important to educate the patient to take it correctly.

CHARISE Good point. Panobinostat; this is a histone deacetylase inhibitor, so HDAC inhibitor. This is the first one that's been approved for myeloma; it's also an oral drug. It does not have single-agent activity; it was approved in combination with a proteasome inhibitor. It was approved with bortezomib, but we are using it with carfilzomib as well on trials. This essentially helps to turn on tumor suppressor genes. This is the PANORAMA trial that looked at panobinostat, bortezomib, and dex versus bortezomib and dex, and the three drugs -- again you see a theme here -- the three drugs were superior to the two-drug regimens.

This is the dosing. Panobinostat is dosed every other day, so day one, three, five, for 2 consecutive weeks. This is how it was approved with a proteasome inhibitor, and you can see the dexamethasone. I'm going to tell you how we do it in clinical practice. This has a lot of GI toxicities, so we have found that our patients tolerate this much better if we dose it every other week. And we can keep them on a lot longer as well.

Side effects -- you want to avoid these fruits. And I think we already mentioned, but with proteasome inhibitors, going back you want to make sure that your patient avoids vitamin C on that. You want to make sure they have antidiarrheals; again, lots of GI toxicities. You want to obtain a baseline EKG for these patients and monitor their electrolytes, and they can have some elevated

transaminases with this and always watch their blood counts. Again, when you look at the GI, the diarrhea -- so when you dose it about every other week, it really helps with that. Fatigue -- again, central theme, some nausea and vomiting, and we do see some fevers with that as well.

This brings us back to our patient. It's a challenge sometimes in the United States when we choose that next line of therapy because most of our patients have been exposed to lenalidomide or maintenance post-transplant. Our patient, though, elected an oral regimen of IRD with ixazomib. He didn't progress on bortezomib. We gave him those four cycles, collected cells, and went to transplant. So it's reasonable to retry the drug on that. He did well for 24 months, and now he's progressing with anemia and bone pain. What treatment at this point would you consider next?

DR. KAUFMAN We're still in this range here. So we still have a group of drugs that we can use, and I would say when we come back here in 5 years, we'll be talking more and more about this group of drugs. From an investigational standpoint, just like we see all over oncology, we're starting to look at things like checkpoint inhibitors, the bispecific antibodies are going to be developed in myeloma, looking at CAR T cells in myeloma, among others.

But what we have now for refractory disease, it's something very exciting in myeloma, is the development of monoclonal antibodies. There are many monoclonal antibodies that have been tested in myeloma and show some efficacy. There are two that are approved, and I'll spend some time talking about them: elotuzumab and daratumumab. They work via multiple mechanisms. For

example, daratumumab, the monoclonal antibody that targets CD38, directly induces apoptosis and we can see single-agent response, and I'll show you that clinical data. But in addition to that, both of these drugs work by enhancing the immune system, either through ADCC or CDC or other mechanisms to upregulate the T-cell component of the immune system. What we've found is that when we use these drugs in combination with the IMiDs, that they can be even more effective.

So from a monoclonal antibody standpoint, a new mechanism of action unlikely to be impacted by the standard resistance mechanisms we see with myeloma in the contents of alkylating agents, IMiDs, and proteasome inhibitors, it can be combined with other therapies. We think because of the relative safety of these medications that we can use it in all settings in myeloma; there are now clinical trials in the smoldering setting, clinical trials using an up-front, clinical trials looking at the maintenance therapy.

From a disadvantage standpoint, obviously, just like we've seen over the past 20 years with the use of rituximab, there are some serious infusion-related reactions; in large part, we can overcome all of that. We don't really know yet from a biomarker standpoint which patient will respond and won't respond. And then, finally, these are very cumbersome and expensive to produce and, hence, they're very costly.

So, elotuzumab -- again, it targets SLAMF7; SLAMF7 is a cell surface protein that lives on both myeloma cells and NK cells. So the hypothesis is that the elotuzumab tags myeloma cells for ADCC and by also targeting the NK cells,

activates the NK cells through NK-dependent destruction of myeloma cells and can be independent of other cellular mechanisms. I'll show you the clinical data that shows its efficacy.

This was some of the first studies looking at combination of elotuzumab len/dex. There was a small study that looked at elotuzumab as a single agent, which did not show efficacy, so we don't think elotuzumab is directly inducing apoptosis. When combined with lenalidomide and dexamethasone, we saw that even in patients who had prior exposure to lenalidomide, there was a high response rate, over 90%, and when we think about lenalidomide and dexamethasone alone, we're looking more like the 60, 70% response rate.

There was then a large phase II study that tried to ask the question, "What's the optimal dose of elotuzumab given with combination lenalidomide and dexamethasone?" And that's what this study looked at, the 10 versus 20 mg dosing of elotuzumab given weekly for the first two cycles and then every other week after that.

What we learned is that there is not a significant amount of excessive toxicity by adding elotuzumab to lenalidomide and dexamethasone. In large part, all of these toxicities that you see in these combination studies are the expected toxicities you see with lenalidomide; the only additional toxicity we see with elotuzumab, again, has to do with the infusion-related reactions.

In a larger study, still relatively small, we saw response rates higher than what we'd expect with lenalidomide and dexamethasone alone. What was very unique about this is that the lower dose of the elotuzumab appeared to be more

effective than the higher dose, suggesting that this was a sophisticated coordination of immune system and not just direct cell kill.

These initial studies led to this large randomized study that's now been published in the *New England Journal of Medicine* last year called the ELOQUENT-2. This was a randomized study for patients with relapse myeloma, one to three prior lines of therapy, and received standard -- both arms received standard len/dex. The experimental arm added the elotuzumab. As you see here, both in this chart showing a median progression-free survival of 19 months versus 15 months, and you see the Kaplan-Meier curve next to it, is that there was a benefit of adding elotuzumab and that benefit was sustained over many years. So this led to the approval of elotuzumab used in combination with lenalidomide/dexamethasone. We are now studying elotuzumab with other IMiDs and in other combinations as well, moving it into the up-front setting.

I did want to point out toxicities. In large part, most of the toxicity has to do with lenalidomide and dexamethasone. There is somewhat more fatigue associated with it, and there are other slightly increased toxicities, but overall, very well tolerated. The big key, toxicity has to do with infusion-related reactions, and most of the infusion-related reactions occurred in the first cycle, some in the second cycle, and very rarely after that. Most of the infusion-related reactions were grade 1 or grade 2, and we do standard prophylaxis with corticosteroids, Tylenol, and Benadryl. We have found because we have patients who were on the original phase I study that we've had patients who've tolerated this for I believe over 5 years. And the patient's still doing very well.

Now, daratumumab, quite frankly, has been the single drug in myeloma that's been associated with the most excitement at least within the myeloma field. I think we all were very excited about it; the reality is is that it is an effective drug, but it's not going to be the final answer for how to manage myeloma. But it has made enormous amount of changes in how we treat myeloma.

It's active, it is a single agent, and I'll show you that data. There is a very good randomized, now published, data that the combination of daratumumab, plus lenalidomide and dexamethasone -- similar to what I just showed you -- is superior to lenalidomide and dexamethasone alone. Most common -- and there's some very unique things about how to manage a patient on daratumumab -- most commonly are the infusion-related reactions.

In the initial studies, as a single agent, there was about a 30% response rate, and that 30% response rate was even in patients who had been refractory to all these other lines of therapy. So in a high refractory patient -- and this is how we communicate with patients -- about one in three patients will respond.

What's interesting is another one-third of patients will have some benefit, but not a formal response, and those patients we'll note also have prolonged survival compared to those patients who have no response at all. So even if it's not responding, there's something about what we believe how it impacts the immune system that carries on after we stop giving daratumumab.

This is a waterfall plot of a small study, 32 patients, who received a combination of daratumumab len/dex. You'll notice of these patients the very high response rate, and if you look at any benefit at all, almost 90% of patients

benefited from this therapy, including a significant percent of patients, a third of patients, achieving a CR. I'll back up one second. I'll mention, just published in the *New England Journal of Medicine* 2 or 3 weeks ago was the daratumumab plus len/dex versus lenalidomide and dexamethasone alone. There was not only a higher response rate, which we would have predicted based on the small study, there was a dramatic improvement in early progression-free survival and way too early to have any predictions about overall survival. So while approved currently as a single agent, the data is very clear that it's very beneficial in combination and then the other combination that we have studied and shown very good responses.

Just looking at this study, numerically it appears that the responses are lower, but remember when we're looking at pomalidomide studies, we're looking at much later in their course of therapy, and these patients were more likely to be relatively early in their course and more of a relapse patient. These patients here are more in the refractory setting and, again, and you can see in the waterfall plot and the data itself you see a very high response rate. Here you see a VGPR rate in a refractory setting with this three-drug combination of over 40%.

I will comment and I know that Charise and our practice knows this, in this and with pomalidomide having a higher incidence of myelosuppression, we have to monitor these patients' counts very carefully. As you imagine the schedule, it's 4 consecutive weeks of daratumumab and 3 weeks of pomalidomide. We see that patient on day 22, and it's very common on that day 22 for the patient to have significant amount of neutropenia, grade 3, grade 4 neutropenia, so we

have to be prepared with growth factors, with supportive care, to support those patients through that period of neutropenia. So I strongly urge you, if you treat a patient on this regimen, pay attention to the neutropenia and think about prophylactic growth factors or growth factor support and prophylactic antibiotics.

In terms of infusion reactions, there are a higher percentage of patients who get infusion reactions with daratumumab compared to elotuzumab; about 50% of patients get infusion reactions with the first dose, it's closer to 10% with the second dose, and very rare with third dose and beyond. Common symptoms -- again, the things that you'd expect -- throat irrigation, cough, dyspnea, wheezing. Very rarely does it cause such severe side effects that a patient has to be hospitalized, and correct me if I'm wrong, I can't remember ever hospitalizing a single patient for a dara infusion reaction.

CHARISE We haven't.

DR. KAUFMAN We probably have treated 400 patients, so we don't expect a hospitalization. But what you need are your infusion nurses to be very aware of how to manage it. Earlier recognition of infusion reactions; holding, re-administering, premedications, Tylenol, Benadryl, corticosteroids. We add the leukatriene inhibitors; it's very important to do that. We found with first dose, we can really minimize serious infusion reactions with the addition of the leukatriene inhibitors.

CHARISE Just to mention -- you want to make sure they get that at least an hour before.

DR. KAUFMAN Then, finally, once their symptoms have resolved, we can restart. We restart and we usually go at half the rate and can often finish that dose in that day.

Other really important points about this is that when in patients because we're measuring, we're trying to measure the patient's monoclonal, their own monoclonal immunoglobin or monoclonal antibody, daratumumab is a monoclonal antibody, and you can detect it on your serum protein electrophoresis. If you don't have a pathologist or you send out to a central lab your serum protein electrophoresis, they're going to be confused and they're going to call daratumumab a paraprotein and there might not be one there. So it's very important that they know that. As Charise mentioned before, in patients who are on almost all of the regimens we think about, varicella zoster prophylaxis. And just one brief comment, we don't give the varicella zoster vaccine. In fact, if you read the package insert, it says myeloma patients can't get it, so don't give it. It's an interesting study, but it hasn't been done yet.

Then the final point about daratumumab is that daratumumab interferes with our ability to do cross-matching, so it's very important that we know that beforehand; it's important that we get a type and screen and we understand what the patient's type is. It's very important that if the patient's traveling, that they have some information that they're on daratumumab, which can interfere with the type and screening and cross-matching. There are ways for your blood bank lab to address that and get accurate typing.

I'll turn it back over to Charise.

CHARISE Back to our patient. We did start this patient on pomalidomide/daratumumab index, thromboprophylaxis due to the pomalidomide, type and screen was sent prior to daratumumab. We also give out cards to our patients that they can carry. We did this on the clinical trials and we do it in our practice. So if they're somewhere else or they're in an accident they've got that information that they're on this antibody.

This patient responded like the data shows you; tolerating and currently responding to therapy. So dara is given weekly for the first two cycles, and then it goes to every other week, and then at cycle seven, it goes to monthly. Again, in clinical practice we do that, but if our patient starts to look like they're losing their response, we'll increase the frequency back on dara again on that. Patients really like that regimen and they're very unhappy when they have to come off of it. It's very well tolerated, especially if they're responding and it's holding them on that once a month treatment.

Myeloma, while it's not curable, the median overall survival has improved dramatically in the past decade, and that's because of all these new agents that we have. The goal of therapy is to improve that depth and duration of response up front and then in that relapse setting get a response, keep them stable. These toxicities are quite manageable, but we do have to monitor closely for these patients, make dose modifications, consider those other comorbidities that they have. And clinical trials, can't say enough about it. It's how we have all these drugs for myeloma.

That's it. We're happy to take questions.

FEMALE This isn't a myeloma question, but it's a CLL. If they're CD38 positive, can we use daratumumab?

DR. KAUFMAN That's a great question. The original phase I study mostly looked at that, and there does not appear to be any efficacy in CLL. There was just a case report that came out -- I want to say it was the NK T cell lymphoma that there was efficacy. So thinking about CD38-positive diseases, I think is the right way to think. It doesn't work in CLL, and I'm sorry I can't remember, but it was some rare T-cell lymphoma that responded and it was just at least a case report on that. That's very, very interesting, but I think looking at CD38-positive diseases and daratumumab treatment will likely be more common.

FEMALE You mentioned no vitamin C with a panobinostat.

CHARISE No, with a proteasome inhibitor. I was talking about panobinostat and went back to that.

FEMALE How long do you go for response to the monoclonal antibodies? When should you see a response? Right away?

DR. KAUFMAN In elotuzumab len/dex, the median time to response was in the first two cycles. I've never seen a patient go from cycle 1 to cycle 2 whose numbers got worse who subsequently got better, so even if they haven't -- and so this is this LO index -- even if they haven't had a response, you'd expect to see some improvement in that first cycle. Having said that, unless the patient's very sick, I would at least give several cycles before stopping a therapy. Daratumumab, in large part, is the same way; if daratumumab is going to work, we're going to see that benefit early.

FEMALE With the thromboprophylaxis, do you use low-dose aspirin, full-dose aspirin?

CHARISE That's a good question. The International Myeloma Working Group recommendations are for somebody who has had no risk factors and have no previous history, so an active patient, aspirin is sufficient. Typically it's a low-dose aspirin: 81 mg. On our clinical trials, frequently we have to give higher doses. For somebody who has another risk factor, they've had a prior clot, you're going to be more aggressive with that; low-molecular weight heparin. There are a lot of the newer agents and we use them in our practice, the newer oral agents, as a rule.

DR. KAUFMAN I would say that the risk factor is to look at -- the two most important risk factors to look at are going to be a prior history of clot or immobility. If these patients have just had some sort of orthopedic procedure because of myeloma and they're in a wheelchair or they spend a significant amount of time a day in bed, then you're going to want to give them more aggressive anticoagulation than just aspirin. The standard risk, again, no history of blood clots, fully mobile, we will give an aspirin; otherwise, we'll give something more; either prophylactic dosing of enoxaparin, the new anticoagulant, or warfarin with a goal INR or 2 to 3.

CHARISE Also, if our patients are traveling -- we have a lot of people that are working and going about life -- if they're traveling on long flights overseas, that kind of thing, then we're a little more aggressive if they're that person who's only on an 81 mg aspirin. There's no data behind it, but it's what

we do. We typically give them enoxaparin the day before they travel, the day they travel, and the day after, and then we're discussing whether we need to do that day after. But that's just because we've seen a lot of that too; they go off on a long flight and come back with a clot.

FEMALE When you're thinking about the monoclonal antibodies in the relapse/refractory setting, is there one you would choose before the other? I think the dara works on the CD38 and the elo works on the other, and I think you would want to use the elo first?

DR. KAUFMAN That's the question that everybody's asking and every myeloma doctor asks it because we don't know the right answer. The general approach -- and I say this as a general approach because nobody's compared this head to head, it's not known if it's true -- but in general, the less aggressive relapses, that earlier asymptomatic rise, are more likely going to choose elotuzumab len/dex. Somebody who has refractory disease or a more aggressive relapse where we really need the highest possible response rate, we're more likely to use daratumumab.

CHARISE We run into the issues because so many of our patients have already progressed on lenalidomide. So I think in our practice, we're probably putting more people on dara because you can just add it in and typically with pomalidomide.

FEMALE We just started using daratumumab in our practice and I'm very interested that you said you use a leukotriene inhibitor for those, so my questions are 1) which do you generally like to use? 2) Do you use the

leukotriene inhibitor for other monoclonal antibodies to prevent infusion reactions? And 3) would you continue using it if the patient hasn't had a reaction by, say, the third treatment?

CHARISE To that last question, we stop. Typically we give it at dose one for both elo and dara. If a patient has a reaction with dose one, then we tend to give it with dose two. We do have a few patients, though, that we've kept it onboard because they need it; they still just have some sensitivity when they receive the drug and they're many cycles out. But it's made a huge difference when we're grading these toxicities; we haven't had anything over grade 2 since we started using it, and we're getting ready to publish some data on that.

DR. KAUFMAN Excuse me for using this name, but we use montelukast and we don't use it in any other case. It's solely with daratumumab.

CHARISE We used to give it when patients were reacting; it was on our protocol when somebody's having reactions they would stop and give it, so then we started --

DR. KAUFMAN Right. But not as prophylaxis.

CHARISE Right. So, it just made sense to start putting it up front to see if it made a difference and it did.

FEMALE I have a question about maintenance therapy with RD. How often do you drop out the D?

DR. KAUFMAN In the maintenance setting after transplant we, in the standard risk patient, we give lenalidomide by itself. If we are using, let's say for example, the study showed in the nontransplant setting they used len/dex until

progression, our typical practice recognizes that in a regimen where you don't have a transplant, in the maintenance portion, that lenalidomide is going to be the more important of the drugs. So, in large part, in the up-front setting, we'll stop it also after the initial induction therapy and go straight with lenalidomide without dexamethasone.

In the relapse setting when we're using a three-drug regimen and you've had a response and you're maintaining remission, it's a little bit less clear about what to do with the dexamethasone. In that setting, we base our dexamethasone dosing on the tolerance of the patient. Instead of having a fixed time when we stop the dexamethasone, we pay attention to what the patients are telling us and stop dexamethasone based on toxicity.

FEMALE With the dex, I have patients complaining all the time that taking 40 on one day drives them crazy, and they're asking me, "Can't I take 5 or 8 every day? Does that make a difference?" When do you start your maintenance lenalidomide after transplant?

DR. KAUFMAN That's a great question and I appreciate you asking it. Every time I've seen patients -- well, I'm going to say it differently -- the efficacy of taking daily dexamethasone is probably the same. The immediate toxicity of spreading the dexamethasone out is obviously better. The long-term toxicity in terms of suppressing the adrenal access is much, much higher when you give it every day as opposed to give it pulses, so I do not let my patients do that. Every time I've ever seen somebody come in cushingoid, it's because they're on daily dexamethasone, so it's very important. We sometimes negotiate it and we let

them split twice a week, but we see long-term toxicity with dexamethasone is much higher when it's given daily as opposed to given pulses. And I forgot the second question.

FEMALE The maintenance question.

CHARISE We risk-stratify our patients, so a standard-risk patient post-transplant we're going to restage at day 100 and then we start maintenance at that point; so lenalidomide single agent. We go to a lower dose on that; typically, it's 10 mg. For our high-risk patients, we do a multidrug regimen and it depends on what the disease is; if they have a 17p deletion, if they have a 414. If they have a 414 translocation, we're going to do something like ixazomib or bortezomib -- single agent on that.

The high-risk patients we had been giving lenalidomide, bortezomib, and dex for a period of 3 years, and then they went to maintenance lenalidomide single agent after that. We're changing and we're doing a lot more now with carfilzomib, pomalidomide in that maintenance setting post-transplant, but we commit them to 3 years of pretty aggressive maintenance. And we have some really nice response rates with that as well. We know single agent will not hold a high-risk patient. Your patient with a 17p deletion, somebody who presented with plasma cell leukemia, they need more aggressive maintenance. We restage those patients at day 60. We don't wait until day 100 because we found we had those patients blasting off with disease by day 100, so we get them in at day 60, restage, and get maintenance going at that point.

FEMALE Do you ever use the lenalidomide plus the new ixazomib?

CHARISE Mm-hmm.

FEMALE Do you ever use that as maintenance together?

CHARISE We do. We have -- again, as patients who want that oral regimen and so we have started doing IRD, so ixazomib/lenalidomide/dex on that.

[END]