Risk Stratification in Multiple Myeloma: Putting the Pieces Together

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FEMALE Good evening, everyone, and welcome to our accredited symposium on "Risk Stratification in Multiple Myeloma." This symposium is accredited by the Annenberg Center for Health Sciences at Eisenhower. To claim your credit, please follow the instructions on the sheet you received this evening. If you did not receive any, please flag us down and we'll bring you one.

We have two wonderful speakers this evening: Dr. Tiffany Richards and Dr. Hans Lee, both from the University of Texas MD Anderson Cancer Center. Dr. Richards is an adult nurse practitioner whose primary research interests include targeted therapies for patients with multiple myeloma. She has given numerous presentations on multiple myeloma and has been published in journals, such as the *Multidisciplinary Cancer Care* and the *Myeloma Messenger*. She is an active member of the International Myeloma Foundation.

Dr. Lee is an assistant professor in the Department of Lymphoma and Myeloma at MD Anderson. He graduated from the Indiana University School of Medicine before his residency at the Washington University School of Medicine. He performed his clinical fellowship in Hematology/Oncology right here in Houston at MD Anderson. His main focus is to broaden our understanding of multiple myeloma and develop better treatments for our patients.

Please welcome Dr. Richards and Dr. Lee.

DR. LEE Tiffany and I would like to thank everyone for attending the satellite symposium this evening. We know that you had many choices potentially

to attend, and we're grateful that you decided to learn more about multiple myeloma.

These are our disclosures. I receive support from Daiichi Sankyo and am a consultant for Takeda Cell Gene in Adaptive Biotechnology. And Dr. Richards is also a consultant for Cell Gene and Takeda.

The objectives of the talk this evening is basically to learn about the factors that go into play when deciding on treatment for newly diagnosed multiple myeloma and to learn more about how we sequence therapies for patients as they progress along in their disease course. In addition, we would like to talk about the common toxicities associated with anti-myeloma therapy, also identify reasons for nonadherence to oral myeloma therapies and appropriate strategies to address them.

And in doing so, the basic outline of our talk, we'll discuss shortly or briefly about myeloma background, then we'll talk about myeloma stratification, and then treatment considerations for both newly diagnosed myeloma, maintenance therapy, and relapse refractory disease. And we'll overview common toxicities to myeloma therapy throughout the talk.

DR. RICHARDS Multiple myeloma is the second most common hematologic malignancy. In 2014, approximately 24,000 individuals were diagnosed with it in the United States. It's twice as common in African Americans than Caucasians and affects a greater proportion of elderly patients and as we can see, over half the patients are diagnosed after the age of 65. Men are more

affected than female, and patients often will sometimes have a family history, prior history of inflammatory or autoimmune condition, or radiation exposure.

Multiple myeloma is a malignancy of the plasma cells, and the plasma cells can lead to bone destruction, which leads to lytic lesions, pathologic fractures, and hypercalcemia. We also can see bone marrow infiltration, which can lead to anemia, thrombocytopenia, and neutropenia. We also see monoclonal globulin, which can lead to renal failure as the light chains obstruct the renal tubules, and approximately 10% of patients we can see a concurrent diagnosis of amyloidosis.

We also see reduced immunoglobulin, so for example, if a patient has an IgG type myeloma, their IgA and IgM levels will often be low and this places them at an increased risk of infection. We know that almost all patients start off with a diagnosis of MGUS prior to their diagnosis. We know that there was a premalignant of primary initiating event, such as an IgH translocation or hyperliploidy. Approximately 1% of patients annually who have MGUS will develop a smoldering myeloma, and those patients with smoldering myeloma will go on to develop symptomatic disease. Most often those patients are at their highest risk of developing symptomatic myeloma within the first 5 years of their diagnosis.

If we look at the diagnostic criteria for multiple myeloma, we can see that the plasma cells should be greater or equal to 10% or a biopsy-proven bone or extramedullary plasma cytoma, as well as evidence of end organ damage, such as CRAB criteria, hypercalcemia, renal insufficiency, anemia, or a bone lesion.

Or they could have one of the biomarkers, the malignancies, such as a greater than 60% plasma cells, a free light chain ratio greater than 100, one focal lesion on MRI that's at least 5 mm in size.

And the biomarkers of malignancy are new in 2014. Prior to that, our indicators for initiating treatment were just a CRAB criteria, and so we've now added those biomarkers. For these patients, it's recommended to start treatment. These are our myeloma-defining events; again, greater than 60% of plasma cells in the bone marrow, a light chain ratio greater than 100, MRI changes, hypercalcemia, renal insufficiency, anemia, and bone disease.

And the one thing that it's important to note that with the renal insufficiency, we want to make sure that it's related to the myeloma. Remember, we're dealing with an elderly population oftentimes and so they can have other comorbid conditions, such as hypertension and diabetes, that can also impact their creatinine. So we want to make sure that we're initiating treatment then for the right reason.

For MGUS, monoclonal gammopathy of unknown significance, this is considered a premalignant condition. Patients will have less than 10% plasma cells in the bone marrow; they should not have any CRAB criteria; and they should have an M protein less than 3 gm in their blood. Their risk of progression to myeloma is about 1% annually.

Smoldering myeloma will have anywhere from 10 to 60% plasma cells in the bone marrow. They may or may not have greater than 3 gm of M protein in their serum, and they should have no myeloma-defining event or CRAB criteria.

These patients will go on to progress to symptomatic disease at a rate of about 10% annually.

The MGUS patients are followed in observation and generally they're followed every 3 to 6 months for the first year and then, annually thereafter. For those patients who have smoldering multiple myeloma, these patients should be followed on observation or be enrolled in a clinical trial for smoldering myeloma patients.

Ms. D is a 59-year-old woman who presented to her primary care physician and was found to have anemia with an elevated total protein. She had normal iron studies, normal vitamin B12 and folate. Her serum protein electrophoresis, however, revealed an IgG kappa M protein of 3.6, and so she was referred to an oncologist. Her workup with the oncologist showed her to be anemic with a hemoglobin of 8.2; she had an elevated creatinine of 4.1; she was mildly hypercalcemic with a calcium of 10.9; her beta-2 M was 9.9; and her platelet count was 514.

Her total proteinuria was 5.5 grams and of that, 4.9 grams were Bence Jones protein urine kappa type, and she had an IgG kappa M protein of 3.7 and she had suppression of her uninvolved immunoglobulins with a low IgA and IgM. Her free kappa light chain was 15,000; her free lambda light chain was 10.4; and she had a kappa lambda ratio of 1,500.

Her bone marrow biopsy revealed 50% plasma cells positive for CD38, CD138, CD56, and positive for kappa light chain. She had normal female

karyotype; however, her FISH showed deletion of 17p and a translocation of 4;14. Her PET and bone survey revealed lytic lesions to the bilateral ribs.

DR. LEE So now that a diagnosis of multiple myeloma has been confirmed in this patient, the next question is how would you risk stratify this patient? Or the other question would be what is the importance of risk stratification in the first place?

As many of you know, there have been tremendous advancements in the treatment of multiple myeloma over the last 10 to 15 years resulting in doubling of overall survival in patients with multiple myeloma during this time period. And this has mainly been due to the development and FDA approval of a number of different myeloma drugs listed here in this slide, most recently panobinostat, daratumumab, ixazomib, and inotuzumab in 2015. And this has resulted in an increase in the life expectancy of standard-risk myeloma patients to 10 to 12 years now.

However, not all patients have benefited to the same degree as standard-risk multiple myeloma, and a subset of high-risk multiple myeloma patients has been identified where prognosis remains poor and survival remains only 3 to 4 years still, despite the use of novel agents. And so why risk stratify myeloma? Well, first and foremost is prognosis, so it's nice to tell your patients, perhaps, what the prognosis of their myeloma would be based on their FISH studies and also identifies a high-risk myeloma patient population that could be candidates for novel treatment approaches, such as clinical trials.

So we define high-risk multiple myeloma using several factors, including disease biology, which is often assessed by cytogenetics and FISH studies, gene expression profiling and sequencing, which is an emerging technology. And this is known as the molecular classification. High-risk phenotypes include plasma cell leukemia and extramedullary disease, which is basically portend to aggressive biology. And laboratory values, such as beta-2 microglobulin, albumin, and LDH are representative of disease burden. And, certainly, response to therapies is also a factor in defining high-risk myeloma; patients who have a very short progression-free survival tend to have a poor prognosis.

So early on in the 1990s when myeloma researchers tried to classify multiple myeloma patients, they relied on more rudimentary techniques, such as convention karyotyping. And so this is a study published back in 1997, which evaluated over 200 patients with myeloma and MGUS, and what they found was that there were frequent abnormalities in chromosome number 1, as well as translocations involving chromosome number 14, 16, and 22.

What is the significance of these chromosomal translocations? So, in this case, for instance, there's a translocation 8;14 on this particular slide. And so basically, these translocations juxtapose, for instance, an oncogene on chromosome 8 c-myc with the IgH heavy chain enhancer on chromosome number 14, which essentially augments the expression of c-myc in the multiple myeloma cells. So this promotes tumorigenesis and potentially more aggressive phenotype.

Also, in the early karyotyping studies it was noted that patients with myeloma often had hyperdiploidy or gains in the numbers of chromosomes, so particular gains in the odd number of chromosomes, as seen in multiple myeloma patients. And so in summary, the earlier molecular classification with karyotyping showed that there are multiple translocations, particularly involving the IgH heavy chain locus on chromosome number 14 and hyperdiploidy in almost 50% of cases.

Later on, a more sophisticated technology came around called fluorescence in situ hybridization, known as FISH, which evaluates for recurrent chromosome deletions, amplifications, translocations, which have prognostic significance. And the standard myeloma translocations, deletions, amplifications that we evaluate for include deletion 13q, 17p, and deletion 1p, amplification of 1q21, and translocations involving immunoglobulin heavy chain locus on chromosome number 14 with partner genes, including 11q, which is cyclin D1; 4p16, which is FGFR3 and MMSET; 16q, which is c-MAF; 6p, which is cyclin D3; and 20q, which is MAFB.

And these studies are not only informative, but they're also prognostic. And so in the era of pre-novel agents, it was noted that cytogenetics had a tremendous impact on the prognosis of multiple myeloma patients. So this is data from the IFM 99 trials, which everyone received increases doxorubicin and dexamethasone as their induction therapy, followed by high-dose chemotherapy and autologous stem cell transplant and, basically, having deletion 13 on

karyotyping, translocation 4;14, deletion 17p, or amplification of 1q21 all confirmed a poor prognosis in these patients.

But, even in the novel agent era, cytogenics and FISH do have an impact on prognosis. And so these are a list of several studies in which bortezomib was incorporated as part of induction and maintenance therapy, such as the HOVON-65/GMMG-HD4 study. And while the introduction of bortezomib is the treatment regimen with patients with translocation 4;14, it definitely improved the outcomes, it didn't completely overcome the adverse prognosis of translocation 4;14, for instance.

So later on some other technologies were evaluated to further molecular classify patients with multiple myeloma. The University of Arkansas pioneered something called gene expression profiling, in which they basically subdivided myeloma patients in seven different subtypes based on their gene expression profiling. And later on, they developed something called the 70-Gene Expression Profile, which was able to predict adverse outcomes. And the study was later commercialized and now is known as MyPRS.

And, finally, sequencing, or gene sequencing, is an emerging technology that we're getting more data from that can help prognosticate multiple myeloma. And this is data from the largest sequencing study to date published in the *JCO* a couple years ago. And, basically, patients with deletion 17p or any abnormalities in the p3 gene, had the worst prognosis in terms of progression-free survival and overall survival on multivariate analysis.

Another way that we re-stratify patients is through the Myeloma International Staging System. Back in 2005, the ISS Staging System was unveiled, which primarily took into account albumin and beta-2 microglobulin levels. And 10 years later, the revised ISS Staging System came out in 2015, which incorporated both the ISS Staging System and FISH studies. And what's important to note—and I think this highlights that—the impact of novel agents in the treatment of multiple myeloma over the last decade, whereas an ISS stage II patient back in 2005 had a median overall survival of 44 months, an R-ISS stage II patient had a median overall survival that basically doubled to 83 months in 2015.

And what's notable is that 95% of patients in the R-ISS staging data received iMiDs such as lenalidomide or pomalidomide and proteasome inhibitors, so this really highlights the impact of novel agents and the natural history and disease of multiple myeloma.

In summary, this is one representative table that the International Myeloma Working Group uses to re-stratify multiple myeloma. Standard-risk patients included those with translocation 11;14, 6;14, or hyperdiploid karyotype. High-risk disease is defined by a number of different translocations and deletions and amplifications, such as deletion 17p; 1q21 amplification; translocation 14;20, 14;60, and 4;14; deletion 13 by karyotype only, not by FISH; high-risk gene expression profiling; hypodiploid karyotype; plasma cell leukemia; and elevated plasma cell proliferation rate.

And there is actually an emerging subset of ultra high-risk multiple myeloma patients that has been identified, and these patients have an overall survival that estimates to be less than 2 years. And these patients have more than three, or three or more adverse cytogenic abnormalities than the high-risk category.

DR. RICHARDS Ms. D is diagnosed with symptomatic multiple myeloma warranting treatment. She has high-risk disease and she is considered to have R-ISS stage III disease. So what are the treatment options for this patient? Prior to 1998, we really had very limited therapy in between the introduction of methylprednisolone in 1962 to 1998, our treatment options really consisted of methylprednisolone, VAD, autologous stem cell transplant, and high-dose dexamethasone.

Thalidomide was introduced in 1998 and between 1998 and 2007, we had the introduction of bortezomib; lenalidomide was approved in 2006; and liposomal doxorubicin in combination with bortezomib was approved in 2007. In 2012 and 2013, we had the introduction of another immunomodulatory agent, pomalidomide, as well as another proteasome inhibitor, carfilzomib. And then, bortezomib was approved to be administered as a subq injection.

And in 2015, we had our first HDAC inhibitor, panobinostat; we had an oral proteasome inhibitor, ixazomib; and then our first monoclonal antibodies were introduced for myeloma, elotuzumab and daratumumab. And so we know about multiple myeloma; it's currently an incurable disease, and patients go in and out of having remissions and then relapsed disease and then back into

remission. But what we also know now is that we have multiple clones at the initial time of diagnosis.

And if you look on the right-hand side, you can see that there is listed four different clones, each different colors. And what we've learned about the disease is that as the patient goes in and out of relapse, that a different clone emerges as the dominant clone until we get to the time that they are refractory disease. And at the time when they're refractory, the clone that was really a minuscule part of their disease at the time of initial diagnosis really now becomes the dominant player.

But there's a lot of great news, we have a lot of treatment options for myeloma, but the problem is how do we choose and sequence these drugs? The first thing we want to consider with a newly diagnosed patient is are they a transplant candidate or not? If they're a transplant candidate, we're going to look at bortezomib/lenalidomide/dexamethasone versus lenalidomide/ dexamethasone. This was a SWOG study where patients were randomized in a 1:1 fashion and they were stratified based on their ISS stage, as well as their intent to transplant. The RVD arm received bortezomib in standard dosing fashion; at that time, it was given IV on days 1, 4, 8, and 11; lenalidomide was dosed at 25 mg on days 1 through 14; and dexamethasone was given the day of and the day after bortezomib.

Patients in the lenalidomide arm received lenalidomide and low-dose dexamethasone in standard dosing fashion, and all patients received aspirin and herpes zoster prophylaxis either with acyclovir or valacyclovir. Upon completion

of eight cycles of therapy, all patients were placed on lenalidomide and dexamethasone. And so if we look at the overall response rates, we can see that the triplet therapy had a higher very good partial remission rate or better. What's most impressive is the CR rate, and in myeloma we know that patients who get into a complete remission have a longer progression-free survival, but also overall survival. And the triplet actually resulted in almost a doubling of the CR rate.

The partial remission rate was similar between both arms and same as stable disease and progressive disease. And so if we look at the overall response rate with the triplet therapy, it was 81.5 versus 71.5 with the doublet. The duration of response was also higher with the triplet therapy; it was 52 months versus 38 months with the lenalidomide/dexamethasone arm.

We look at their progression-free survival, again, the triplet regimen had a higher progression-free survival. And then, if we look at the high-risk patients, those patients on the triplet arm did much better than those who were on lenalidomide and dexamethasone. And if we look at specifically translocation 4;14, we can see that receiving bortezomib/lenalidomide/dexamethasone doubled their progression-free survival. Again, if we look at overall survival, again, the triplet arm did much better than those who received lenalidomide and dexamethasone alone.

Now, if we look at bortezomib/lenalidomide/dexamethasone and compare that to bortezomib/cyclophosphamide/dexamethasone, the IFM did a phase III study and patients were randomized in a 1:1 fashion to receive either

bortezomib/thalidomide/dexamethasone or to bortezomib/cyclophosphamide/dexamethasone. Both cycles were repeated every 21 days, and then upon completion of four cycles of therapy, patients were able to receive high-dose chemotherapy, followed by autologous stem cell transplant at the discretion of their treating physician.

We look at the overall response rate we can see that there's a higher very good pressure response rate or better in those patients who received a proteasome inhibitor in combination with an immunomodulatory agent. Now, granted, here in the United States we don't really use thalidomide much anymore, but what we do know is that lenalidomide has a much higher response rate than thalidomide, and so we could make the assumption that using lenalidomide with bortezomib would be better than using bortezomib/ cyclophosphamide/dexamethasone. If we look at the stable disease or better, those were also similar in both arms.

There was a retrospective review that compared both regimens in patients with high-risk disease. And so again, if we look at the arm that received a proteasome inhibitor in combination with an immunomodulatory agent, we see a VGPR rate that was significantly higher than the VGPR rate or higher in the VCD arm. Additionally, the CR rate was significantly higher at 23% versus 8% in those who received bortezomib in combination with an alkylating agent.

If we look at survival in high-risk subgroups and randomized trials with bortezomib in newly diagnosed myeloma patients, we can see that those patients who received a proteasome and they received bortezomib with their treatment,

had a much longer overall, 3-year overall survival than those who did not receive the proteasome inhibitor.

And now, we have carfilzomib. So investigators moved carfilzomib to the up-front setting in combination with lenalidomide and dexamethasone. And both Jakubowiak and Korde both did phase II studies with carfilzomib/lenalidomide/dexamethasone. Carfilzomib was dosed in both studies at 20 mg/m^2 on days 1 and 2 and then dose increased to 36 mg/m^2 on subsequent days. They received eight cycles of therapy and then subsequently, they went on to a maintenance phase. In the Korde trial, they went on to receive lenalidomide 10 mg on days 1 through 21, and in the Jakubowiak study they received carfilzomib every other week with lenalidomide at their last tolerated dose.

The Jakubowiak study allowed patients to go on to stem cell collection and high-dose chemotherapy, followed by autologous stem cell transplant, whereas in the Korde study they received stem cell collection alone and did not have the option to go on to transplant.

So if we look at the overall response rate, we can see that they had a 62% near CR/CR rate in the Jakubowiak study, and similarly, Korde also found a 56% near CR/CR. Korde actually looked at minimal residual disease in patients and found that 67% were negative by NGS. And if we look at the very good partial remission rate or better in both studies, we can see it was about 98%. The progression-free survival at 2 years in the Jakubowiak study was 92% and then

the Korde study at 18 months was 92%. So, again, very high response rates, as well significant progression-free survivals.

If we look at the response rates for car/len/dex, we can see that at least 100% of patients with stage I and stage II disease received a PR or better, was 100%. Those with stage III disease, their PR or better was 93%. And then, if we look at standard-risk disease, if we look at the response rate, standard risk was 100% versus those with unfavorable disease was 94%.

There are currently ongoing additional studies in multiple myeloma for newly diagnosed. There is bortezomib/lenalidomide with up-front or delay autologous stem cell transplant; there's an ECOG study that's comparing VRD versus CRD; a SWOG study that's looking at elotuzumab for high-risk patients, and so patients will be randomized to VRD with or without elotuzumab; and then, there's an ongoing study—it's a phase III—where patients are being randomized to receive VRD with or without daratumumab.

So what about our older patients? This was the FIRST study; it was in patients who were elderly and were nontransplant eligible. Patients were randomized in a 1:1 fashion to one of three arms. They were randomized either to MPT, to lenalidomide and low-dose dexamethasone continuously, or to lenalidomide and dexamethasone for 18 months. Patients were taken off for progressive diseases or unacceptable toxicities. If we look at the response rates, we can see that the overall response was between the continuous Rd and the Rd18 were similar; however, if we look at the MPT arm, it was much lower than what we saw with lenalidomide.

If we look at the CR rate, both arms, as well as lenalidomide arms, had similar CR rates; however, the MPT was only 9%. The time to response was much faster in those patients who receive lenalidomide compared to those who received MPT; however, the duration of response was much longer in those who received continuous lenalidomide compared to those who received lenalidomide/dexamethasone at 18 months. And as you can see, the Rd18 and the MPT actually had similar durations of response. If we look at the progression-free survival; again, the lenalidomide/dexamethasone continuous did better than those who received Rd18 or MPT at 25.5 months.

So how do we decide what we're going to treat our patients with? If they're transplant eligible, we recommend a triplet regimen, such as bortezomib/lenalidomide/dexamethasone, which is the standard of care currently. You may want to consider carfilzomib/lenalidomide/dexamethasone in those patients with high-risk disease. In the transplant-eligible patients, you definitely do not want to give melphalan because melphalan can impact your ability to collect stem cells. For those who are transplant ineligible, you could consider a doublet, such as lenalidomide/dexamethasone or you could use a triplet therapy, such as bortezomib/lenalidomide/dexamethasone based upon the patient's frailty, as well as their comorbidities, and then, they should receive maintenance after initial therapy.

So if we look at our older patients, we know that the Charlson Comorbidity Index actually helps to predict 10-year mortality for patients by looking at their scores and assigning a score for their comorbid conditions and age scores by

assigning points to factors. And so in the frail patients, you'd really want to consider using a doublet instead of a triplet therapy; these patients most likely would not be stem cell transplant candidates. And then, you also want to consider using lower doses, such as what Palumbo has recommended.

This looks at all of the drugs that we have available for myeloma, and it looks at what risk factors do they have? If they have no risk factors, you would dose them at the regular dose level; however, if they have more than one risk factor you would want to dose reduce them. For example, lenalidomide you would take down from 25 mg down to 15 mg a day, and bortezomib instead of using on days 1, 4, 8, and 11, you'd want to move that to days 1, 8, and 15 of a 35-day cycle. If they have one risk factor and they experience a grade 3 or 4 non-hem adverse event, you'd want to dose them even lower. So it's really important that you look at the patient in front of you; look at their comorbidities; look at their frailty; and then make adjustments to their therapy.

If we look at the side effects that we see with proteasome inhibitors, almost all therapies for myeloma cause fatigue. And so when we're assessing fatigue, we want to rule out other causes of fatigue, such as depression, hypothyroidism; you want to instruct them on energy-sparing activities; and then you also want to try and get them to get involved in an exercise program. And oftentimes, if my patients have peripheral neuropathy or they have a lot of pain, I'll refer them for aqua therapy because aqua therapy is really good for patients; it takes the weight off their bones; they can move around more. Because you want

them doing some sort of activity because we know that cancer patients do benefit from physical activity.

For gastrointestinal affects, approximately a third of patients will experience either diarrhea or constipation, so you want to make sure that patients have both either Imodium or Miralax or Senokot or something similar on hand for if they get diarrhea or if they get constipation. If they develop thrombocytopenia, we generally would not hold therapy unless their platelets go below 25,000. And even then, it's really important in myeloma patients to consider their bone marrow infiltration.

So, for example, if you have a patient who has 90% plasma cells in their bone marrow and they're starting off with a platelet count at 50,000, well, you can assume that they're going to go below 25,000. And so rather than holding therapy, you'd want to transfuse them up and then continue on therapy because the only way you're going to reduce their marrow infiltration is if they continue on treatment. Because otherwise, the disease is just going to get worse and you're never going to get ahead of the game, so you really want to take that into consideration with your patients.

For cardiac events for carfilzomib, you want to ensure that you obtain a baseline echo prior to carfilzomib, so that if they would develop dyspnea in the middle of therapy and you get a repeat echocardiogram and they have a reduced EF, you know what their EF was beforehand, because otherwise you're kind of out there stuck saying, "Well, was this from drug or wasn't it from drug?" And this way, if you have a baseline echo and their EF reduces, then you would know if it

was from that or not. You also want to make sure that patients know to report increased dyspnea and not to just sit home and say, “Okay, I’m short of breath; I’m not going to the ER and I’m not going to tell anybody, I’ll wait until my next visit because I’m going to see them in 2 weeks.”

If they develop peripheral neuropathy—and while we see that less with carfilzomib and ixazomib, it’s still really important that we’re educating patients about peripheral neuropathy. And I generally try not to use a lot of descriptors when I’m talking to them about peripheral neuropathy because I find that if I tell patients it’s numbness, tingling, and burning sensation and they’re experiencing like they’re walking on rocks, they may not report it because, “Well, she didn’t tell me to call if I felt like I was walking rocks; she only said numbness, tingling, burning,” or whatever descriptors you choose to use. So I’ll usually tell patients, “Take note of what your hands and feet feel like right now and if that changes, then call so that I can assess you and determine if this is something that we need to be concerned about or if this is something that I’m not too concerned about.”

If they are developing peripheral neuropathy, you really need to ensure that we dose adjust right away. We tend to think about grade 1 as not being that big of a deal, but if we think about what grade 1 neuropathy is, it’s like having your leg be asleep all the time. And we all know how annoying that is when your hands or feet go to sleep, right? You’re like shaking it off and you're trying to get it to go away and it drives you crazy. And that’s only for a maybe a minute at the most, right? So imagine that all time, 24 hours a day; you’re trying to go to sleep and your feet feel like that or your hands feel like that. So if we can dose adjust

early, then we can prevent that from getting worse. We also want to educate patients on the signs and symptoms of neuropathy, as I mentioned.

For herpes zoster, there is an increased incidence with the proteasome inhibitors, so we need to make sure that patients are on either valacyclovir or acyclovir prophylaxis. And then, also making sure that they're still taking it when they come in for the follow-up visit. I can't tell you how many times patients run out of all of their refills and they're like, "Well, I didn't have any more refills left, so I just stopped taking it." And you're like, "Oh, my goodness; no, you need to keep taking it. You need to call and make sure."

Renal insufficiency we can see with carfilzomib, so these patients will receive IV fluids prior to their dose. Just be careful with the amount of IV fluids because you don't want them to get fluid overload. Generally, at our center we only give 250 cc before the carfilzomib and that's it, and patients do really well with that. You want to make sure that you're looking at the creatinine clearance and dose reducing ixazomib for creatinine clearance less than 30 cc. And then, again, you want to monitor their renal function with carfilzomib.

We know that patients with cancer are at an increased risk of thromboembolic events; they're at about four- to five-fold increased risk. Their risk of mortality is also higher than in the normal population, and patients with advanced disease are at a higher risk of thromboembolic events. And, generally, myeloma patients are at their highest risk of developing a thromboembolic event at the time of their initial diagnosis because their tumor burden is so high. So we want to make sure that when we're starting a patient on an immunomodulatory

agent in combination with a steroid that we're looking at their risk factors and that we're replacing them on anticoagulation appropriately.

This is just a risk assessment model, so if they have no risk factors or only one risk factor, then you can place them on an aspirin a day. And we have to remember that myeloma counts as one risk factor, so if they even just one more risk factor, we would actually want to place them either on full-dose warfarin or low molecular heparin provided they're not at a risk for a bleed. So we don't want our patients who are falling all the time to be on warfarin or something, so to take that into consideration.

The risk factors that they identified were obesity, a prior clot, comorbidities, such as diabetes, renal disease, if they have immobilization, if they're taking medications, such as erythropoietin. And then, it's also important to make sure that we're re-evaluating as we go along. So, for example, you may have a newly diagnosed patient who arrives to your clinic; they have a lot of compression fractures, they can't walk because they have so much pain. But go ahead 2 or 3 months later, their pain's under control, they're out of their wheelchair, they're up walking around, so maybe they don't have as many risk factors now and maybe that immobility risk factor is taken down, and so maybe you could take them down to an aspirin. So, again, it's always really important that we re-evaluate and re-assess the patient.

And then, obviously, we want to make sure that we educate patients on the signs and symptoms of VTE and then, also, educating them on what they can do to help prevent a clot, right? Patients are always asking, "What can I do to

help my disease?" And whenever they ask that, I say, "Well, what you can do is you can move around more, make sure that you're getting up and walking if you're on a long car ride. If you're on an airplane ride, you need to get up and walk around, draw the alphabet with your feet." Those sorts of education things are really helpful for patients so that they can be proactive in their care.

And then, myeloma is also really complicated because we have both oral as well as IV medications, right? So we have patients that may be coming into the clinic for their subq shot or their IV medicine, but then they're also on oral medicines, and sometimes they may be on a completely all-oral regimen. And so how do we ensure that our patients are taking their medications and taking them correctly? So it's important that patients understand that they're always going to be on therapy, that most likely patients with myeloma are not going to have a period of time where they're not on therapy. We know that patients who stay on therapy and receive therapy live longer and that patients know that if the pill's sitting in the bottle or at the pharmacy, that is not going to do anything to those myeloma cells, right?

It's important that patients are involved in their treatment decision making, so encourage them to be involved, be involved in the process. If there is a possibility between two regimens, they may prefer, "You know what? I may live less, but I don't want that side effect," so involve them. Also, encourage them to report their side effects. I can't tell you how many times a patient when they're progressing from their disease will say, "Oh, do you think that not taking that dexamethasone made a difference?" And it's like, "Yeah." So if they know that

they can report that and that you aren't going to get mad at them because they're not taking their medication, it encourages good dialogue.

Also, if they're reporting their adverse events, then we can dose modify. A lot of times patients don't want to tell us what side effects they're experiencing because in their head if they tell you about a side effect, you're going to reduce their medication. And if they equate, "If my medication's reduced, then I'm not going to live as long. I'm not going to have as good of a response." So it's really important that patients understand that if we can keep you therapy, even if it's at a reduced dose, that that's better than you not taking your medication periodically or skipping doses because we know that that is not going to help the patient.

We give our patients calendars to help them to know when to take their medication, so if they're on an all-oral regimen, such as ixazomib and lenalidomide and dexamethasone, they take their lenalidomide every day for 21 days; they take their ixazomib on days 1, 8; 15, they take their dexamethasone on days 1, 8, 15, and 22. So how does a patient keep that altogether? And remember, we're talking about older patients. We have an older patient who's getting chemo, who may have some memory problems because they're taking the chemo, plus they're on steroids, so all these things go together to make it really, really imperative that patients know and understand when to take their medication. And then, also, to engage caregivers in the treatment process and then, also, just to talk about how encouraging patients to talk about how they're feeling about being on therapy.

If you've had myeloma for 10 years and you've been on therapy for 10 years and always on chronic therapy, that's a really, really long time to be on therapy. And they get tired of it. So at least if they're voicing that to you, then you can potentially talk about treatment breaks. Say, "Hey, do you need a treatment break?" And you can have that conversation. Now, mind you, if their disease is out of control, that's not going to be the time that they're going to get their treatment break, but if the disease is doing well and it's stable, then you can have that conversation with patients.

Other barriers to adherence is going to be financial. If a patient's on ixazomib and lenalidomide, that's two high co-pays. And if they're on Medicare, that's probably about $800 a month if they have Part D and if they don't have any co-pay assistance. And we know that the co-pay assistance programs are running out of money much faster now, so it's getting harder and harder for patients to receive that, so we need to keep those things in mind. Also, if they're older, they may have impaired executive function. And then, also assessing for depression because if they're depressed, they may not want to take their medication, and so making sure that we're assessing for that.

Other ways to tailor treatment to patients' specific comorbidities: if they have pre-existing neuropathy, you may want to consider using our carfilzomib-based regimen versus a bortezomib, as there is less neuropathy with carfilzomib. If they have pre-existing cardiomyopathy, you could consider a bortezomib-based regimen versus carfilzomib, as approximately 5% of patients who receive carfilzomib can develop congestive heart failure. If they're in renal failure, you

may consider bortezomib/cyclophosphamide/dexamethasone initially to get the rapid response. If they have diabetes, you want to make sure that you're engaging their primary care provider and endocrinologist to help you manage the steroid-induced diabetes and making sure that you get a hemoglobin A1C at the start of therapy. If they're borderline diabetic, you know those patients are going to go into full-blown steroid-induced diabetes, so it's better to know that ahead of time rather than waiting until it comes on full onset.

And if they have a history of bleeding, such as a gastrointestinal bleed, you may want to avoid using an iMiD with dexamethasone and instead, consider a proteasome inhibitor with an alkylating agent, so that you can avoid the need for thromboprophylaxis.

Ms. D starts carfilzomib/lenalidomide/dexamethasone as her frontline therapy and develops a pruritic, raised macular rash after she starts therapy. So how would you advise the patient? Similar to the side effects with proteasome inhibitors, the one difference is the risk of rash; approximately 10 to 25% of patients do develop rash.

What we use at our center is we will stop their lenalidomide and we'll start them on cetirizine, ranitidine, and L-lysine. And oftentimes, you can continue them at the same dose level and they will not have a rash again. So you want to hold therapy, wait until the rash resolves, and then when you restart the lenalidomide, start those three drugs together, and your patients will often be able to continue at their same dose level.

The other difference would be the thromboembolic events, as I mentioned before. And then, it's important to remember that both with lenalidomide and pomalidomide, there are dose reduction guidelines for impaired creatinine clearance, so it's important that we're checking our creatinine clearance in patients with myeloma. Because when you look at their creatinine clearance, I would probably tell you that 7 out of 10 times they're not going to have a normal creatinine clearance level, so make sure that you're checking it and dose reducing according to the recommendations.

DR. LEE Ms. D completes four cycles of carfilzomib/lenalidomide/dexamethasone for her high-risk multiple myeloma and she has a very good partial response. She's now ready to proceed to high-dose chemotherapy and autologous stem cell transplant, and she asks you in clinic, "Well, what is the potential benefit of undergoing an autologous stem cell transplant?" And this is a question I get frequently in seeing myeloma patients in the clinic, and this is a question that myeloma researchers and clinicians have also been debating amongst themselves for many, many years.

There's been some thought that with the novel agents that have been introduced at the myeloma therapy armamentarium that, "Well, is stem cell transplant really, really necessary?" Because the benefit of stem cell transplant was observed back in the 1990s when we were using older agents, such as the anthracyclines or vincristine, dexamethasone, melphalan, and prednisone. Probably the most recent and best study that has tried to address this question is the IFM/Dana-Farber study, in which, basically, transplant-eligible patients with

newly diagnosed multiple myeloma were randomized 1:1, to either receive RVD for three cycles, followed by autologous stem cell collection with cyclophosphamide mobilization, five additional cycles of RVD versus RVD, then moving forward with autologous stem cell collection, high-dose chemotherapy, autologous stem cell transplantation, followed by RVD consolidation for two cycles.

And in the IFM 2009 part of the trial, which was done in France, patients received lenalidomide maintenance therapy for 1 year. It's important to note that in the Dana-Farber arm of the study, which has not been reported yet, patients received lenalidomide maintenance indefinitely.

In terms of overall response, overall response rates did favor the transplant arm slightly in terms of the depth of response; 86% VGPR versus 78% VGPR in the RVD arm. But overall response rates total were pretty similar; 99% in the transplant arm and 98% in the RVD arm. In terms of progression-free survival, it was noted that patients who underwent up-front high-dose chemotherapy and stem cell transplant had improvement to progression-free survival of about 14 months compared to those that underwent a delayed stem cell transplant approach. Although overall survival at the time of follow-up did not differ between the two groups, suggesting that patients who deferred on their initial stem cell transplant could be salvaged by stem cell transplant later on in their disease course.

In terms of the high-risk subgroup of patients, it seemed that patients benefited from high-dose chemotherapy and stem cell transplantation up front

regardless of their ISS stage. And, also, patients had standard-risk disease and there's a trend towards benefit in the high-risk disease, but this was less pronounced compared to the standard-risk patients.

In terms of up-front transplant versus delay transplant, evolving questions include the role of indefinite maintenance with lenalidomide and long-term outcomes. Remember, that in the IFM 2009 trial, patients only received 1 year of maintenance lenalidomide, so it'll be interesting to see if the progression-free survival is impacted by indefinite lenalidomide maintenance therapy. So the role of MRD negativity is a clinically relevant endpoint in deciding on up-front versus delayed autologous stem cell transplant.

And I mentioned this because the American Society of Hematology abstracts were just released earlier this week, and there is a study that's being presented by the French group, which is the final results of the impact of MRD testing using highly sensitive next-generation sequencing with the sensitivity of 10^{-6} on outcomes in the IFM 2009 study. And what the abstract text says is that there was no difference in progression-free survival as long as the patient achieved MRD negativity if they underwent an up-front stem cell transplant versus delayed stem cell transplant approach. So this presentation will be highly anticipated at the ASH meeting later in December.

But, in 2017, there is no data to support that high-dose chemotherapy and autologous stem cell transplant is the standard of care, so as a general practice in all transplant-eligible patients at MD Anderson, we generally refer patients to

the stem cell transplant group for consideration of autologous stem cell transplantation.

Ms. D proceeds with high-dose chemotherapy and autologous stem cell transplant and she returns to the clinic 2 and a half months post-transplant and is a near CR, and she's here to discuss maintenance therapy options with you. So what do you advise about maintenance therapy for this particular patient? The concept of the maintenance therapy has been around in myeloma for quite some time, initially with trying agents such as interferon-alfa and thalidomide, which were generally poorly tolerated as long-term maintenance strategies due to the side effects of the drugs.

Back in 2012, there were two landmark maintenance clinical trials published in the *New England Journal of Medicine* evaluating lenalidomide maintenance therapy in the post-transplant setting. The CALGB trial basically took patients 3 to 4 months post-transplant and randomized patients to either receive lenalidomide or placebo. And it's important to note that lenalidomide was started at 10 mg once a day initially and then, potentially dose increased to 15 mg once a day as long as they're tolerating the 10 mg dose well from a cytopenia standpoint.

In terms of progressive-free survival, the patients who received lenalidomide maintenance therapy had improved progression-free survival by about 19 months compared to the placebo arm. And this 3-year overall survival rate also favored the lenalidomide maintenance arm compared to the placebo arm.

Likewise, the IFM 2005-02 study also showed that lenalidomide maintenance therapy was beneficial for patients in the post-transplant setting, showing an improved progression-free survival by about 18 months compared to the placebo arm, although overall survival did not differ between the placebo and the maintenance arm in that particular study.

Importantly, lenalidomide maintenance therapy did seem to benefit patients with high-risk cytogenic abnormalities, such as deletion 13q by karyotyping and patients with translocation 4;14 and deletion 17p, although it was less significant in the high-risk subgroups compared to those without the high-risk cytogenic features.

It is important to know and counsel patients that there is a risk of secondary malignancies with lenalidomide maintenance therapy in both the CALGB trial and the IFM trial. There is about a 2 to 2.5 increased risk of developing secondary malignancy, either other blood type tumors, solid tumors, or non-melanoma skin cancers.

I did want to briefly mention to you of the strategy of potentially using both an iMiD and a PI as maintenance therapy for high-risk multiple myeloma patients. Because generally, I think it's thought in the myeloma community that probably lenalidomide may not be enough, particularly in patients with high-risk multiple myeloma, as the overall survival and progression-free survival in these patients is still very poor in the high-risk patient population.

The Emery Group published a study several years ago looking at RVD maintenance for the high-risk multiple myeloma patients in which patients after

autologous stem cell transplant received the RD maintenance for 3 years. Patients in this particular study had high-risk features, including deletion 17p, deletion 1p, translocation 4;14, 14;16, plasma cell leukemia, and other aggressive presentations. And what they found was that the use of RD maintenance did improve the depth of response after stem cell transplant in this high-risk cohort, but, also, the progression-free survival was quite encouraging in some of these high-risk subgroups, including those with deletion 17p had a pretty similar overall survival compared to the rest of the high risk in the particular cohort. And the overall survival in this particular patient population with deletion 17p was very good at 3 years.

So based on the high-risk phase II data out of Emery, Ms. D started bortezomib/lenalidomide/dexamethasone maintenance therapy given her high-risk disease, and 1 year later she develops a painful vesicular rash over her T9 dermatome, and the diagnosis of zoster is made. And upon further questioning, she stopped taking her antiviral prophylaxis 3 months ago. So which myeloma drug likely contributed to her increased risk of varicella-zoster?

I know Tiffany already touched on this, but the risk of herpes zoster is increased in patients receiving proteasome inhibitors, including bortezomib, carfilzomib, and ixazomib, so it's important to educate patients on symptoms of zoster, including the fact that the rash typically occurs over a dermatomal distribution.

DR. RICHARDS Ms. D returns to the clinic for follow-up. After 2 years on maintenance therapy, she is found to have a reappearance of her M protein at

0.5. So what would you recommend for treatment? These are just different definitions for relapsed disease, both clinical relapse in which we not only see an increase in the M protein, but we also see appearance of CRAB criteria, such as hypercalcemia, renal insufficiency, or even the development of new soft tissue plasma cytomas or bone lesions.

The definition for relapse from a complete remission just means that their immunofixation could become positive now. And it doesn't mean that they have a measurable M protein; it means their immunofixation is not positive or they may have more than 5% plasma cells in the marrow.

And then, for progressive disease we define that as a greater than 25% increase with an absolute value of 0.5. For the urine protein electrophoresis, a 25% increase with an absolute value of 200 mg. And then, patients who only have light chain disease, we would see the difference between the involved and uninvolved free light chain levels and that absolute increase must be greater than 10.

So what treatment do we choose? The first thing we need to ask is what is the goal? What are the previous therapies they had? How did they respond to those therapies? What toxicities did they experience? What characteristics and other factors are they having? So if they were in remission for 10 years, they were diagnosed at the age of 70, they're now 80, they could have a completely different set of comorbidities, and you want to make sure you're taking that into consideration. And then, are there clinical trials versus standard of care?

These are the NCCN preferred regimens for first relapse, and as you can see, the majority of them are triplet therapies or a doublet of carfilzomib/dexamethasone. So if we look at a carfilzomib, the APSIRE trial randomized patients, to receive carfilzomib/len/dex or two len/dex. Patients were randomized 1:1 and they were risk stratified based on if they had prior lenalidomide or prior bortezomib. And as we can see, the patients who received the car/len/dex had a longer progression-free survival compared to those who received lenalidomide/dexamethasone alone.

If we look at the high-risk subgroup analysis, we can see that those patients who had high-risk disease did better with a triplet therapy compared to the doublet. For example, if we look at the deletion of 17p, their median progression-free survival was 24.5 months and the standard-risk disease was 29.6 months. So what we can take from this study is that particularly for patients with high-risk disease, they do benefit from the triplet therapy compared to just lenalidomide and dexamethasone alone.

The ENDEAVOR trial randomized patients to carfilzomib/dexamethasone versus bortezomib/dexamethasone; again, patients were randomized in a 1:1 fashion. It is important to remember that the carfilzomib-arm patients were dose increased to 56 mg/m^2, so it is to take that into consideration that they were not increased to 27 mg/m^2.

If we look at the response rates in both the standard risk, as well as the high-risk disease, we can see that both the high-risk patients had a high complete remission rate of 15.5% with the carfilzomib group compared to only

4.4 with bortezomib. If we look at the duration of response, it was higher with the carfilzomib arm in both the standard risk, as well as the high-risk disease, and similarly the progression-free survival as well.

If we look at the high-risk subgroup, if we look at high risk who received Kd versus those who received bortezomib/dexamethasone, there was not a statistically significant difference between the groups; however, there is a difference between those who had standard-risk disease.

There is another phase III trial that compared ixazomib/len/dex versus len/dex; again, patients were randomized in 1:1 fashion to receive ixazomib 4 mg on days 1, 8, and 15, or lenalidomide, and patients could be dose reduced based on their creatinine clearance for the lenalidomide in this trial, and the cycle was repeated every 28 days. If we look at the progression-free survival, we can see an improvement in the patients who received ixazomib compared to those who received placebo. The median progression-free survival is 20.6, as opposed to 14.7 months in those who received the placebo.

If we look at the subset analysis, we can see that the benefit was seen across all high-risk subgroup types. If we look at the median progression-free survival, those patients who received lenalidomide who had deletion of 17p was 21.5 with a duration of response of 20.5 and a time to progression of 21.4. So ixazomib/len/dex is also another alternative for patients who have high-risk disease, as this trial definitely showed a benefit of ixazomib compared to placebo.

It is important, again, to make note of the risk of peripheral neuropathy with ixazomib, although if you look here, the incidences of all grades, peripheral neuropathy was 27% in the ixazomib arm and 22% in the placebo arm, so that's a little bit higher than what we would expect to see in lenalidomide/dexamethasone. I think it's important to note that all patients receiving therapy should be educated on the signs and symptoms of neuropathy and educated for prompt reporting.

We know that neuropathy is common in myeloma and is present in approximately 75% of previous treated patients. The etiology of it is not clear, but it's thought it could be due to direct damage to nerve cells, toxicities to the dorsal root ganglion, or decreased nerve blood flow. So it's important patients are monitored at each visit and that they know to report their symptoms early.

It is important when we're assessing for neuropathy not just to take the patient's word for it. We need to do our physical exam and look at how they're walking, test their muscle strength, making sure that they're able to use their fine motor moments. Because as we all know, patients like to hide their symptoms and they will hide their peripheral neuropathy just as much as they will hide their fatigue or any other symptoms. In fact, I think they hide their peripheral neuropathy more than their fatigue.

I've oftentimes have patients tell me they're doing fine, and I get them up on the exam table, I do my assessment, I go to check for peripheral edema, I touch their legs, then they're practically jumping off the table because they're in pain. And I'm like, "Wait a minute; I thought we weren't having any problems?"

They're like, "I'm not, it's just a little painful." So, again, it's just important to do that.

As far as treatment of neuropathy, it's important, again, to intervene early and to dose reduce appropriately. If we're using bortezomib, we want to use subcutaneous bortezomib rather than IV, as we know the incidence of peripheral neuropathy is less with a subq. You could consider the use of glutamine. There was one study that showed that there was a benefit in using glutamine in patients as a preventative.

We want to make sure that we're checking for vitamin B12, B6, and folate deficiency because those can cause peripheral neuropathy. And then, depending on the severity, we can consider initiating gabapentin, pregabalin, or duloxetine. Duloxetine's great if you have somebody who you think might have some depression in addition to their peripheral neuropathy.

You can consider acupuncture. We did a study at our center and approximately 50% of patients did have a benefit with acupuncture. So that's something that you could try using in a patient who maybe is hesitant to use medication or you're concerned about adding any additional medications.

You'll want to consider a pain management specialist and a physical therapist. And, again, in a patient who had peripheral neuropathy, you may want to consider aqua therapy and physical therapy. And then, also, it's important to educate our patients on the precautions that they need to take, similar to what we would do with a diabetic patient who has peripheral neuropathy.

DR. LEE So moving on to other treatments for relapsed refractory multiple myeloma, the monoclonal antibodies, including elotuzumab and daratumumab have represented a significant advancement in the treatment of multiple myeloma over the last couple of years. Elotuzumab is a monoclonal antibody that binds to an antigen called SLAMF7. And it's important to note that in the early phase I/phase II studies of elotuzumab single agent, there was no objective responses, so don't give single-agent elotuzumab. But later on they combined elotuzumab with immunomodulatory drugs, such as lenalidomide, and they did see responses.

And primarily, elotuzumab acts through ADCC—antibody-dependent cell-mediated cytotoxicity—muted by natural killer cells. So basically, elotuzumab augments NK cell activity and it leads to plasma cell killing through the NK cells. And lenalidomide augments the action of the NK cell, as well, which is why we see the therapeutic affect when combining elotuzumab with lenalidomide or pomalidomide.

Elotuzumab was FDA approved in combination with lenalidomide and dexamethasone through the ELOQUENT-2 trial and I'm going to go through these pretty quickly. And, basically, in summary, patients who received elotuzumab/len/dex had a higher overall response rate to say, 9% versus 66%, than those that just received lenalidomide and dexamethasone. And importantly, progression-free survival in the elotuzumab arm was improved by about 5 months at 19.4 months compared to len/dex, which had a median PFS of 14.9 months.

It's important to note that the affect or the benefit the elotuzumab/len/dex was also seen in high-risk multiple myeloma patients between those with deletion 17p and translocation 4;14. In terms of infusion-related reactions, they can occur with the elotuzumab, which can be anything from fevers, chills, flushing, shortness of breath, headaches, dizziness, and rash. This occurs in about 10% of patients who receive elotuzumab and we give patients appropriate pre-medications prior to the elotuzumab infusion, including oral dexamethasone 28 mg 3 to 24 hours prior to their elotuzumab infusion.

Daratumumab is a monoclonal antibody against CD38, which is expressed on plasma cells. And the mechanisms of daratumumab are diverse, including ADCC, which was also seen in elotuzumab, but, also, ADCP, which is antibody-dependent cellular phagocytosis, and CDC, which is complement-dependent cytotoxicity. It has a tremendous effect on the immune system and augmenting their response of daratumumab in myeloma patients.

Daratumumab was approved as a single agent back in 2015, in which is showed about a 36% overall response rate in heavily pre-treated patients, those that were prior refractory to proteasome inhibitors and iMiDs and those with more than three lines of prior therapy. And this led to combination studies with daratumumab, including those of bortezomib and dexamethasone, known as the CASTOR study. And this randomized study basically demonstrated that the combination of bortezomib, daratumumab, and dexamethasone had improvement of overall response rates of 83% compared to bortezomib and dexamethasone alone at 63%.

And the progression-free survival was not available at the time of follow-up when this particular study was published last year in the *New England Journal of Medicine* and was 7.2 months in the bortezomib/dexamethasone arm. The hazard ratio was fairly impressive at .39, with a confidence role of .28 to .53.

In addition, daratumumab has been investigated in combination with lenalidomide and dexamethasone in the POLLUX study. And in summary, there was a significant improvement of overall response rates in the daratumumab/len/dex arm at 92.9% versus 76% in the len/dex arm. And in terms of the median progression-free survival, it was 18.4 months in the len/dex arm and it was actually not reached in patients in the daratumumab/len/dex arm at the time of follow-up when this study was published.

Common reactions to daratumumab can include neutropenia, diarrhea, upper respiratory tract infections, and cough, which were noted to be higher in the daratumumab containing arm compared to the control group in the POLLUX study. Fatigue and nausea are also things to watch out for with daratumumab.

About 40 to 50% of patients who received their first dose of daratumumab will have an infusion-related reaction, which decreases to less than 5% in patients starting with their second dose of daratumumab. There are important ways that we can try to mitigate the risk of infusion reactions in patients receiving daratumumab.

The first thing that we like to do is we like to check pulmonary function testing in all patients receiving daratumumab. It is important to note that in the registration stage with daratumumab, those patients with a FEV1 of less than

50% were actually excluded from these studies because they had a higher risk of pulmonary complications. Once we decide that a patient is a candidate for daratumumab, we administered appropriate pre-medications, including antipyretic, H1/H2 antihistamines, methylprednisolone, and an oral leukotriene receptor agonist, such as montelukast. Montelukast can reduce the risk of infusion-related reactions by about one-third, so I would recommend administering montelukast in all patients receiving daratumumab. And in patients with a FEV1 of less than or equal to 80%, administer a beta-2 agonist, such as albuterol.

And in terms of post-treatment, we give steroids, such as dexamethasone and methylprednisolone. Dexamethasone 4 mg once a day for 2 days after each daratumumab dose when it's given as a single agent, or you can give 20 mg of IV dexamethasone on the day of daratumumab and on the day after the daratumumab, as per the POLLUX study, when used in combination with lenalidomide or pomalidomide.

It's also important to note that the use of monoclonal antibodies have their own sort of important guidelines for laboratory testing, so daratumumab is notably known to interfere with RBC compatibility testing. I'll go into this in more detail in just a second, but it's important to notify the local blood bank that the patient is going to start daratumumab or anti-CD38-based therapy. And it's important to perform RBC phenotyping or genotyping prior to administering daratumumab, and it's important to monitor closely for reactions when patients are receiving a red blood cell transfusion.

When a patient is typed and screened, pre-typed erythrocytes are basically dropped into the patient's serum and the pre-typed erythrocytes contain various antigens. And in the absence of any antibodies circulating the patient's serum, when the anti-IgG ratio is added, there'll be no agglutination. But in the presence of antibodies present in the patient's serum, you'll see agglutination on the type and screen.

When daratumumab is present in the serum—I'll get through these here—and actually CD38 is expressed on RBCs, basically, daratumumab will bind to the CD38 expressed in the RBCs and cause a false-positive. It will cause agglutination in patients getting a type and screen, so you won't know the actual patient's type and screen because it'll always be positive. So hence, you see agglutination when the pre-typed erythrocytes are added to the patient's serum.

So in order to get around this, there are a couple different strategies. One way is you can potentially give DTT, which basically denatures CD38 expressed on the erythrocytes. You can also potentially give soluble CD38 to basically bind to circulating daratumumab in the patient's serum, so it won't bind to CD38 on the RBCs. Or you can add an anti-idiotype antibody to bind to daratumumab circulating the patient's serum and, hence, it won't bind to the CD38 expressed in the RBCs. So the most simple way to try to get around this is just make sure you get a type and screen on a patient before you start daratumumab.

Other considerations are the interference with SPEP and immunofixation in patients receiving monoclonal antibody-based therapy. Both elotuzumab and daratumumab are IgG kappa M proteins and so they're monoclonal proteins. So

if your patient has an IgG kappa myeloma, then potentially you see some circulating daratumumab expressed on the SPEP. So there are ways to potentially get around this, including a daratumumab interference reflect assay, which his used for clinical trials. Basically, you have an anti-idiotype IgG antibody that binds to daratumumab and it shifts the migration of the gel, and this way you can discriminate between the patient's endogenous M protein and the circulating daratumumab in the blood.

One other consideration is that sometimes with daratumumab-based therapy, CD38 expression will be decreased in plasma cells, and so this can alter flow cytometry results that are used to identify plasma cells on bone marrow biopsies. So sometimes you may have to use other markers of plasma cells besides CD38 to identify such plasma cells on bone marrow biopsies.

There are a number of different side effects potentially with monoclonal antibodies, but the main being, again, infusion-related reactions, so just make sure they're administered appropriate pre-medications. And, again, I want to encourage everyone to use oral leukotriene receptor antagonist, such as montelukast, prior to daratumumab infusion.

DR. RICHARDS If we look at pomalidomide and dexamethasone, this was the MM-003 study where patients were randomized to pomalidomide/dexamethasone versus high-dose dexamethasone. And this really is the high-risk level group analysis. And if we look, we can see that those patients that received pomalidomide who had deletion of 17p did have an improvement in their progression-survival compared to those who received high-

dose dexamethasone. And similarly, we saw the same thing with translocation 4;14, indicating there may be some activity for our benefit with pomalidomide in high-risk myeloma.

If we look at, again, the overall response rates as we look at the translocation 4;14, as well as deletion of 17p, with pomalidomide and dexamethasone in high-risk disease, we can see a benefit. And we can see that those patients who had deletion of 17p who received pomalidomide actually did a little bit better than those patients who had translocation 4;14.

If we look at carfilzomib/pomalidomide/dexamethasone, this was a phase I/II study where patients were placed on carfilzomib at 20 mg/m^2 and then dose escalated to 27, they received pomalidomide for 21 days with dexamethasone once weekly. And if we look at the response rates, we can see that the response rates in patients with deletion of 17p was actually 80%; it was actually a little bit higher although it was a small subgroup of patients, only five patients that have deletion of 17p. However, nevertheless, it does show that this regimen does have some activity in high-risk myeloma.

When we're working with patients who have myeloma, we want to be sure that we're aware of their risk of infection. So if we look at patients who have myeloma, 45% of patients had early deaths and it was due to infections. So we really want to make sure that we're aware of this risk. They're at increased risk of bacterial infection at a seven-fold increase and a 10-fold increase in viral infections. And this risk could be due to their hypogammaglobulinemia. They could have lymphocyte dysfunction; neutropenia. They may be on steroids, which

can cause hyperglycemia. They may have kyphosis due to their compression fractures, so they're not able to expand their lungs. They may have other comorbidities, such as COPD, renal failure, and diabetes.

And then, their antimyeloma therapy can place them at risk for infection, and grade 3 infections can range anywhere from six all the way up to 21% in some studies. And then, they also have a diminished response to vaccines, so while we give them the influenza vaccine, they're not going to have the same response that somebody that doesn't have myeloma has. So as far as infection risk, you may want to consider using IVIG monthly in patients who are having repeat infections. We use that in our patients, and we oftentimes will see reduced infections.

They may require antibiotic prophylaxis, so if you have a patient who is on therapy and they keep getting repeat infections, that may be somebody you want to put on some prophylactic antibiotics. Depending the regimen, if it's more myelosuppressive, then those patients definitely should be on something prophylaxis.

You want to make sure that they're on an antiviral prophylaxis when they are receiving a proteasome inhibitor or a monoclonal antibody. They should receive their vaccines, but they should not receive any live vaccines; so no shingles, yellow fever, or intranasal influenza. If they underwent autologous stem cell transplant, you want to make sure that they receive their post-stem cell vaccines. And then you want to make sure that they're getting their influenza vaccine and that patients understand that the flu year goes from September to

September. Because if you ask your patient, “Did you have your flu shot this year?” And they had it in March, they’ll be like, “Oh, yeah, I had my flu shot this year.” But they really didn’t have it this year; they had it last year. So patients are going to understand what you mean by that.

You want to make sure that they’re up to date on their pneumonia shot, both their pneumococcal as well as their PCV. And if they’re going to get their influenza shots from a pharmacy, you want to make sure that they’re bringing you a copy of that because they’re not given any sort of immunization records when they get their shots at pharmacies. So you want to make sure that they’re bringing you a copy of that.

They should know that good handwashing is important and that they should avoid being around people who have signs and symptoms of illness. And I’ll, in fact, tell my patients who maybe go to religious services to wear a mask so that they don’t have to shake hands with the people around them, so that they don’t have to worry about offending anybody. Because the last thing a patient wants to do is offend somebody by saying, “I don’t want to shake your hand.” So, I tell them, “If you wear a mask, that’ll indicate that there may be something wrong with you and it’s best for the other person not to shake your hand.”

If traveling outside of the country, it’s important that they meet with ID specialist to find out what immunizations that they need and what prophylaxis they should be on.

In summary, treatment for relapsed refractory myeloma, there’s a lot of different options available for myeloma and it’s really quite overwhelming to

patients. I had a patient once who had relapsed after 15 years and when we laid out all the options, she was just looking at me like, “Oh, my God. Like seriously, you're giving me all these options?” So it’s good news that we have a lot of options, but it can be overwhelming.

If they’re having an asymptomatic biochemical relapse, you may want to consider watching weight if they have standard-risk disease. But if they have high-risk disease, you want to make sure that you’re intervening early because those patients are not going to sit; they’re going to take off. When they start relapsing, they take off very quickly.

If they are having a biochemical relapse, it does offer you more flexibility to consider a doublet or an all-oral regimen. If they’re having an aggressive clinical relapse, you may want to consider a daratumumab or a carfilzomib-based regimen. And then, again, we want to make sure that we’re tailoring our treatment and balancing its therapeutic efficacy with the patient’s quality of life and make sure that we understand what the patient’s goals of care are.

The landscape for myeloma therapy is rapidly evolving. It’s important to risk stratify patients at diagnosis so that we can have novel treatment approaches for patients with high-risk disease. For frontline therapy, we want to make sure that we’re determining are they eligible for transplant or not. Triplet therapy is preferred over a doublet therapy for transplant-eligible patients. And the role of up-front stem cell transplant continues to evolve, but it’s still considered the standard of care today.

For patients for maintenance therapy, for those with standard-risk disease, we want to use lenalidomide maintenance; however, in those patients with high-risk disease, you may want to consider a proteasome inhibitor in combination with lenalidomide and dexamethasone.

For relapsed refractory myeloma, again, it's important to define the type of relapse are they having. Is it just biochemical or are they having CRAB criteria, are they having bone lesions, cord compressions? And then, let that help you to guide your choice of therapy.

And, again, it's important to intervene early in patients who have high-risk disease because these patients will take off very, very quickly; and, again, tailoring therapy to our patient.

DR. RICHARDS Okay, so I think we're open for questions now.

DR. LEE Yes, this wraps up the presentation, so --

DR. RICHARDS Any questions? No? Oh, there's one.

FEMALE From your presentation about the type and cross, I had heard separately that there was something the blood bank could do to knock those antibodies off there and get a good type and cross.

DR. LEE Yeah, briefly I probably mentioned—I went through it pretty quickly—but there are ways to potentially mitigate that artifact. So you can potentially add an anti-idiotype IgG to the patient's serum.

FEMALE Right, to the patient's sample; got it.

DR. LEE The patient's serum and this will bind to the circulating daratumumab, and then they won't bind to the CD38 on their RBCs.

FEMALE I was thinking you were talking about treating the patient with that though.

DR. LEE Right, right.

FEMALE Okay, gotcha.

FEMALE My question is about the glutamine; what's the dose and frequency, and do you do a trial and reassess if it's effective or not to how long?

DR. RICHARDS Yeah. It was a phase I study. I can't remember the dose of the glutamine off-hand, but if you give me your email address, I can get that for you. It was a really small study, but it could be something you could consider. I don't remember, but I have the study at home, so I just don't remember the dose off-hand. But I can get that to you if you give me your email address.

FEMALE And you found it effective in clinical practice?

DR. RICHARDS I have not used it myself, but I know at the Cleveland Clinic Beth Faiman did a study where she placed patients on glutamine versus placebo, and those patients who received he glutamine actually did have less neuropathy than those who received the placebo.

FEMALE Okay, thank you.

FEMALE The risk stratification is done at diagnosis; do you ever do it again with all these relapses and changes?

DR. LEE Yeah, that's a great question. Yes, I think it's very important to get intermittent bone marrow biopsies on patients and constantly evaluate the patient's underlying FISH panel because we know that clinical evolution can

occur in multiple myeloma patients. So, for instance, if a patient has an earlier than expected relapse after their stem cell transplant, but their original FISH was normal, then I would definitely first just get a bone marrow biopsy because a deletion 17p could have evolved in the interim.

DR. RICHARDS And I would also add if you have somebody who is developing like extramedullary disease, oftentimes you can order the FISH panel on that tissue. Because if you do a bone marrow, sometimes they may not have a lot of plasma cells in their bone marrow anymore because it's all extramedullary now. So if you order the cytogenic studies on the soft tissue plasma cytomas, you can get it from those other sites as well.

FEMALE I was just going to speak from experience on the glutamine. I've used it for years and I swear by it. It doesn't work with everybody for sure, but I've seen it really help a lot of people. And it's good to hear that at least some study has been done. But, like I said, I've used it on hundreds of patients and it works well.

DR. RICHARDS That's good to know.

FEMALE They take it three times a day ideally, but sometimes that's too often for them to want to do it that often. But that's how it works the best.

FEMALE (Inaudible).

FEMALE What was that?

FEMALE (Inaudible).

FEMALE I haven't noticed any side effects. Some people don't like the taste or—it's a powder, so they just don't like taking it. But, no, I've never noticed any side effects. I've also used it for mouth sores and it's helped some people.

FEMALE (Inaudible).

FEMALE What?

FEMALE (Inaudible).

FEMALE I think it's ten three times a day. I think it's grams, not milligrams. Yeah, 10 gm. And I always have to tell people it's over the counter. It's at health food stores, and it's not at drugstores.

DR. RICHARDS Oh, there's a question over there. Oh, I think --

FEMALE (Inaudible) or is there a difference in the efficacy of the two?

DR. LEE Can you just repeat the beginning of the question?

DR. RICHARDS Can you repeat it? We didn't hear you.

FEMALE Do people use lenalidomide versus pomalidomide just a dealer's choice, or is there increased efficacy with the pomalidomide versus lenalidomide in high risk versus standard?

DR. LEE Yeah. The last slides that Tiffany presented there did seem to be a benefit of pomalidomide particularly in patients with high-risk myeloma and deletion 17p. Pomalidomide in general is considered more potent than lenalidomide and is able to overcome lenalidomide resistance in certain patients. I think the main thing is getting pomalidomide approved by insurance and you can't use it in earlier settings because it's likely not going to be approved by the insurance companies.

I would say in practice, I still have a philosophy that we have a number of drugs for the treatment of multiple myeloma, but there's still a finite number of drugs. So I really like to exhaust each drug as much as possible before moving on to a next-generation one, so just give a personal vignette of what I would considered.

Let's say a patient's on lenalidomide maintenance therapy after stem cell transplant; 10 mg once a day. I'll probably still continue some type of lenalidomide-based combination in the relapse setting, either ixa/len/dex, elo/len/dex, carfilzomib/len/dex, dara/len/dex, but potentially increase the lenalidomide dose from 10 to 25, add the dexamethasone, add the third agent.

Because sometimes you see the synergy between the iMiDs, for instance, then daratumumab or elotuzumab, and so it's my philosophy to really maximize every drug. And you really want to know when the patient is going to respond anymore before moving on to the next treatment regimen. Because if you burn through them too fast, then you'll be left with nothing in the end.

DR. RICHARDS Right.

FEMALE Thank you so much for coming everyone.

[END]