Integrating Best Practices to Improve Outcomes in Relapsed/Refractory Multiple Myeloma

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BARBARA ROGERS: Good afternoon. We're going to go ahead and get started. We want to thank all of you for coming to the CE-certified satellite symposium entitled, "Integrating Best Practices to Improve Outcomes in Relapsed/Refractory Multiple Myeloma." This symposium is supported by educational grants from Celgene Pharmaceuticals, Janssen Biotech, Inc., and is administered by Janssen Scientific Affairs, LLC, and Oncopeptides, Inc. I'm Barbara Rogers, and I'm a member of the APSHO Education Committee.

I want to introduce our speakers for today: Ms. Amy Pierre and Dr. Joshua Richter. Ms. Pierre is a nurse practitioner at Memorial Sloan Kettering in New York where she serves as an expert hematology nurse practitioner in caring for patients with lymphoma and multiple myeloma. She received her master's degree in nursing from Yale School of Nursing where she was also awarded a scholarship by the American Cancer Society for academic achievement and contribution to oncology care. Dr. Richter is an assistant professor of medicine at the Icahn School of Medicine at Mount Sinai and also works at the Tisch Cancer Institute in the myeloma division. Dr. Richter is also a member of the International Myeloma Working Group and has served as a principal investigator and sub-

investigator in numerous clinical trials. Please help me in welcoming both of them to the program.

AMY PIERRE Thank you so much, Barbara. It's a pleasure to be here. Good afternoon, everyone. So today we're going to talk a little about integrating best practices to improve outcomes for our patients who have relapsed/refractory myeloma, but before we get started, of course we want to know a little bit about you. Here are our disclosures as well. So we're going to talk a little bit about the mechanism of action of current therapeutics that are approved for relapsed or refractory myeloma, also some of the novel new drug targets that are coming out down the pipeline. We're going to look at the clinical trial data that supports a lot of these approved drugs as well as the emerging drugs on the market coming up. We're going to look at strategies for selecting therapies and sequencing them appropriately and figuring how to manage these treatment-related adverse events.

All right, so I'm going to turn it over to Dr. Richter to give us a little bit of Myeloma 101 to talk a little bit about the epidemiology about the disease and a little bit about what's coming up too.

Dr. JOSHUA RICHTER Thank you, Amy. Thank you everyone – wow, lots of you – for being here; very much appreciated. Thank you, JADPRO and everyone. So what is myeloma? And I think this is something that we get asked by our patients at the bedside all the time, and I think because a lot of the people who develop myeloma, they're the first ones in their family to even hear about the disease; it's a big step. A lot of our patients have very easy ability to understand

colon cancer, lung cancer, but they say, "Well, what is myeloma?" And essentially what I tell my patients is that, although this is 2019 and we know all these facts about genetic drivers of cancer and immunologic drivers, we still call cancers by whatever cell becomes malignant. So a skin cell becomes malignant, it's melanoma; a lung cell becomes malignant, it's lung cancer; myeloma is a malignancy of plasma cells, and plasma cells are immune antibodies, and under normal circumstances, immune cells make antibodies to fight infection. In this case, unfortunately, it's making a messed up protein. So when we send these for protein electrophoresis, we're looking at all the different types of protein in people, and the one on the left shows a normal SPEP, where that area of the bump all the way on the right of that, that's a normal polyclonal mix. You have a little bit of an antibody to fight the flu, and one to fight shingles, and so on and so forth; all the different types. But you have a group of plasma cells that are all the same, they're all related to each other, they all make the same bad protein, and we measure that on the right with that big spike. So how does this actually work? And I will not take credit, I borrowed these slides from Dr. Cole, who's an amazing physician. So normal protein electrophoresis, we're going to put some plasma on it, and we're going to charge it. So, put some plasma on, charge the plate and shoot an electric charge across, and then all the proteins are going to leave out there from the heaviest to the lightest. So you get the gamma region, the beta, alpha, and albumin, and this is really what we do when we're looking for these abnormal spikes, and the gamma zone is where the antibodies live, normal ones and abnormal. So what happens when we have all the different types of

plasma cells making antibodies to fight all different types of infection? Because there are many of them, it's polyclonal, normal one. What happens when it's abnormal? Well, we run it through the same process. We run the electric charge through, and then in this region that's supposed to be polyclonal, we find this one big spike of protein, way more than the rest of them, and that's the monoclonal protein or the M-spike. So we have the plasma cells, they pop up, they're all related, they all make the same bad protein, and that's what we measure, is the M-spike in the blood. Then what we do is we give some type of treatment, and many of the treatments we give today kill the bad cells in the marrow, and then the protein levels go down. So we're actually just measuring things in an indirect way, the protein levels go up and down as opposed to measuring the bone marrow plasma cells every time. I think our patients would really not like it if we did bone marrows every cycle of therapy to see what's going on. But ultimately, what we know about myeloma is that it's not one disease. When you think about many cancers, we think about a solid clone or a single clone – leukemia, lymphoma. Myeloma we know at the time of diagnosis, most patients with myeloma already have four to six subclones of disease, and as you go through treatment, those become dominant or recessive, and it's not just the body attacking the clones and/or drugs attacking the clones, but the clones fight each other, which is sometimes why you can have a person with a very indolent disease and then all of a sudden you give some therapy, and they relapse like crazy because you killed one of the clones that was holding the other bad clones under control. And not only do we have intrapatient variability, we have

interpatient – or the other one way around – so this is a patient that we had that had a plasmacytoma that was biopsied in the spine in a regular bone marrow, and the genetics come out completely different. You know we have a low risk versus a high risk, hyperdiploid versus non-hyperdiploid, MEK/BRAF driven, so really the only thing that we can use about this is that this is why we constantly recommend multiple mechanisms of action to kill the cells. This is why triplets and even quadruplets have become the standard because one or two drugs may only control some of the clones; more drugs, as long as you can get them in there, with toxicity, will control more of this. And I think I will pass it back over to Amy Pierre.

AMY PIERRE That's a really important concept to think about because I always tell my patients, the disease you have today is not the disease you had 5 years ago, and that's really because of the whole concept of clonal evolution; your disease evolves over time. And so what is relapsed disease in myeloma? Well, we know it's really people who are on therapy, they're doing fine, and then all of a sudden, we have a reappearance of that CRAB criteria, so that's C standing for that hypercalcemia, that R for the renal insufficiency, that A for the anemia, or the B of the bony lesions, and attributable specifically to the myelomas. So not hypercalcemia because something's wrong with your parathyroid, or anemia because you're iron deficient; it has to be truly attributable to the multiple myeloma. Or you have a plasmacytoma, which is a tumor collection of those abnormal plasma cells, that's either enlarging or you have a new number of them, so that's all people really no longer responding to therapy.

Or also another definition of relapsed disease is your disease has completely gone away, you achieved the complete remission, but now we have a reappearance of those abnormal proteins either in the bone marrow or even we see the abnormal proteins in your blood or in your urine, or a development of that CRAB criteria I was speaking of. So what we knew way back then, you know, when Dr. Richter was practicing a long time ago – I'm kidding, I had to do it – I had to do it. So what we knew way back then is that if you really weren't responding to those kind of early generation drugs, so lenalidomide and thalidomide, the earliest form of the immunomodulatory drugs, or bortezomib, which was kind of the first on the market, proteasome inhibitor, your progression-free survival is looking pretty dismal measured in only a short order of months, and your overall survival the same. Then we came up with some new therapies, right? We had the approval of carfilzomib, which is a second-generation proteasome inhibitor, and pomalidomide, which is a second-generation immunomodulatory drug. But we knew if you progressed on those lines of therapy as well, your median overall survival is roughly about 8 months, so then we get the monoclonal antibodies, daratumumab and elotuzumab, but now we're doing so great with myeloma, patients are living longer and longer that they're becoming refractory to these new novel agents. So they're becoming what we call penta-refractory, so they're refractory to all those proteasome inhibitors that we're hitting them with, all the immunomodulatory agents, and now our new fun monoclonal antibodies that we were so jealous of our lymphoma colleagues for having monoclonal antibodies, now we have the myeloma, but we're having

patients becoming refractory to them as well. That class of patients, the penta-refractory patients, look at their overall survival; it's measured in only a short order of months, so we need new targets to combat this problem. So we have several unmet needs in myeloma, right? The multiply relapsed, the penta-refractory population needs a lot of help. The elderly, you know, myeloma is a disease of the advanced age. The average age of diagnosis is about 69. We, of course, see a lot of young patients at the myeloma centers that we have, but the average age is 69, and we have patients living very long years up into their 80s and they have a lot of comorbidities, so it's a difficult patient population to treat. And then of course, our patients who were getting on bortezomib way back in the day intravenously, you have a lot of peripheral neuropathy, or a lot of pain from their bony lesions. We really need to figure out better ways to manage the pain and the peripheral neuropathy that we see a lot with our patients, and of course, a cure. We want to – right now, myeloma is not a disease that we can cure. We think of it as a chronic disease that we can beat down with medicines, but as Dr. Richter talks about, it comes back over and over again and different each time, so we really need to figure out a cure for our patients. And another unmet need is our African American myeloma patients. So myeloma is the second most common hematologic malignancy in America, second to non-Hodgkin's lymphoma, but for African Americans, it's the number-one blood cancer for African Americans, and it's one of the malignancies in our country that has the greatest disparity in incidence and prevalence. We see that some studies actually show there are biologic differences in the disease presentation and

manifestation in African Americans versus caucasians, so we know that African Americans with myeloma have less deletion 17p, which is that tumor suppressor gene, which really can be a poor prognostic indicator for a lot of different cancers; myeloma is no different. So we see actually less deletion 17p in African Americans, but we do see a lot more CRAB criteria in African Americans in the setting of kind of a low level of that monoclonal protein, which is counterintuitive to what we think. We would think if you have a really high M-spike, a lot of that disease burden, you would have a lot of that CRAB criteria, but we're seeing low levels of that M-spike, but high evidence of end-organ damage in African Americans. So we see more hypercalcemia, more renal insufficiency, or anemia, but interestingly enough, we see less fractures in African Americans, and that's pretty much because in the orthopedic literature we see that African Americans tend to have better bone density than caucasians. We see higher LDH, more requirements for hemodialysis for African Americans, so there's a big population there who are in need, and studies have shown that African Americans are less likely to get the novel therapeutics that are pretty much standard of care in this country, so they're less likely to get bortezomib, they're less likely to get lenalidomide, they're less likely to get a stem cell transplant, which we know can be kind of the gold standard for care for myeloma, and they get, you know, referred to stem cell transplant delayed, less likely to participate in clinical trials. But research now shows that if we give American Americans treatment in this kind of equal access system, so access to those novel therapies, get them to

stem cell transplant on time, they actually achieve equal if not better outcomes than caucasians, so we have a lot of work to do for that disease population.

So let's talk a little bit about the current therapies that are approved on the market for multiple myeloma. So we have our immunomodulatory drugs; thalidomide, lenalidomide, and pomalidomide are proteasome inhibitors. Bortezomib, carfilzomib, and ixazomib are classic chemotherapy agents, the anthracyclines and the alkylators, and then steroids, every patient loves to hate the steroids; it's the backbone of pretty much every myeloma regimen that we use. We have our histone deacetylase inhibitor, panobinostat; our monoclonal antibodies, elotuzumab and daratumumab; and now our newly approved this past summer, selinexor, our XPO1 inhibitor.

So I'm going to talk a little bit mostly about the drugs that we only use in the relapsed/refractory setting because thalidomide and lenalidomide we can use upfront, but pomalidomide is exclusively for the relapsed/refractory setting, and it's indicated to be given in combination with dexamethasone for patients who have received two or more prior lines of therapy including lenalidomide and a proteasome inhibitor or 60 days within the last therapy showing progressive disease, and it's also approved to be in combination with elotuzumab. So what is the main difference between lenalidomide and pomalidomide? We know that pomalidomide is more potent than lenalidomide, but why is that? So they have a different chemical structure, we know. There is a much higher affinity to cereblon with pomalidomide than lenalidomide, and we know that cereblon is the big mediator for a lot of the immunomodulatory drugs. We know that low-level

expression of cereblon can have a little bit of a better prognostic feature, but it really can confer resistance to the immunomodulatory drugs. We do see that there's different degradation kinetics between lenalidomide and pomalidomide. There's a much rapid or faster downregulation of those oncogenes, and it can activate more than 7,000 different genes than lenalidomide, and in terms of overcoming lenalidomide resistance, pomalidomide does that by direct tumor killing and also distinct immune activation of the T cells and natural killer cells. How do we dose it? So basically, pomalidomide is dosed 4 mg Days 1 through 21, you get a 1-week break on a 28-day cycle, and we can use pomalidomide in the context of renal insufficiency, which is important because a lot of our patients develop renal insufficiency – the R in the CRAB criteria – when they relapse. But if a patient is on dialysis, we do need to dose reduce it by 25%. None of our cancer patients should be smoking, but with pomalidomide, definitely not; it can reduce the efficacy of pomalidomide. And lenalidomide is dosed 25 mg, it's the standard dosing; in the maintenance setting, it's dosed at 10 mg. Lenalidomide is renally cleared, so you do have to dose reduce for renal insufficiency, and thalidomide has a variety of dosing. What do we need to think about when we're treating our patients with pomalidomide or any of the immunomodulatory drugs because they share a lot of the same side effect profile. There is a risk for embryonic and fetal toxicity, so unfortunately, thalidomide in the 1950s was given to pregnant women to help with morning sickness and insomnia and caused horrific birth defects, so now there's a black box warning for all the immunomodulatory drugs because lenalidomide and pomalidomide are synthetic

analogs of thalidomide. So patients need to be participating in a REMS program, so they have to sign their life away – no, I'm kidding. They have to do phone surveys every month, they have to adhere to contraceptive use. Women who are female, childbearing potential, have to adhere to the pregnancy testing, so providers and patients both have to enroll in this program. Immunomodulatory drugs can increase your risk of developing clots, fatigue is common with pretty much all myeloma agents. The immunomodulatory drugs can cause a functional rash; it's not really a true allergy, and it can happen pretty quickly too, so we basically hold the drug when people have this itchy rash, it can be on their scalp, it can be on their trunk, on their extremities, and it's really, really easy to get rid of if you hold the drug for a couple days and support the patient with antihistamines and topical steroids, and usually when you re-introduce the immunomodulatory agent, the rash actually doesn't really come back. Myelosuppression we can see at varying differences with all these different drugs. Pomalidomide tends to cause a lot of neutropenia. Thalidomide really doesn't cause very much myelosuppression and GI distress. They are oral agents, so they can cause a little bit of stomach upset, either constipation or diarrhea, depending on the agent. So how do we prevent this? Make sure we're ensuring REMS compliance for our patients, monitoring their blood counts of course, infection precautions. We need to renally dose for lenalidomide, and of course a risk assessment should be individualized for each patient about their risk for developing a VTE. And just this year, it was published in the JNCCN, a new risk model for immunomodulatory associated venous thromboembolism, and it actually

outperformed the current NCCN Clinical Practice Guidelines for risk stratification for clots, and it's really easy, and we're going to give you a lot of acronyms today, so this is one of them. So SAVED is the acronym, it's based on five easy clinical factors, so Surgery – I think it's surgery within 90 days buys you 2 points; Asian race, minus 3 points; a personal history of clot buys you 3 points; being elderly, so 80 or above, buys you a point; and then we know that the risk of immunomodulatory-associated clots really is in combination with dexamethasone, so either you're getting high-dose dexamethasone, that gives you 2 points; standard dexamethasone gives you 1 point; really easy to figure it out. If you have 2 or more points, you're at high risk for a VTE with your IMiD, and it's really important for this patient to be on full anticoagulation, either with low-molecular-weight heparin or a DOAC or warfarin. We tend to use DOACs because they're much easily tolerated; it's just a pill, you don't have to really do laboratory monitoring, versus something simple like a baby aspirin.

Now proteasome inhibitors, we know – I like to think of proteasome inhibitors as kind of a garbage disposal breaking down those proteins. They're protein recyclers, and they degrade unneeded and damaged proteins to maintain that protein homeostasis, and we know that cancer cells are more dependent on the proteasome for clearance of abnormal proteins, and they're really sensitive to proteasome inhibition, and how they work is they inhibit proliferation of myeloma cells, and they induce apoptosis of myeloma cells, and they also affect the bone marrow microenvironment and help prevent the adherence of the myeloma cells to the bone marrow stromal cells. And myeloma, these are monoclonal proteins,

so the myeloma is highly dependent on the proteasome for cell cycle survival. So bortezomib was approved to be given in newly diagnosed and relapsed, but carfilzomib and ixazomib are pretty exclusively right now in the relapse setting. So carfilzomib is a second-generation proteasome inhibitor; it differs from bortezomib by binding to the proteasome irreversibly. So this is intravenously; it's approved to be given at first relapse in combination with lenalidomide and dexamethasone or as monotherapy or in combination with dex. Depending on the dose, it can be infused over 10 minutes or 30 minutes. It can be given twice a week or at higher dose once weekly. Ixazomib is an oral proteasome inhibitor, and it's similar to bortezomib. I always think of it as bortezomib's cousin. It's approved to also be given at first relapse in combination with lenalidomide and dexamethasone, and it's a pill that's dosed once weekly, so you really need to ensure patient compliance; it's very easy to forget taking a pill that you only have to take once a week, and you do have to take it on an empty stomach, so either an hour before you eat or 2 hours after.

So what do we need to think about when we're giving our patients carfilzomib? We can see some myelosuppression with this drug, particularly thrombocytopenia, and it's very cyclic in nature. We can see it around Day 8 or 15, and by the time the patient comes back from their next cycle, their platelet count has pretty much normalized back to their baseline. We can see a little bit of constipation or diarrhea. We can see this cough or shortness of breath phenomenon with carfilzomib. Sometimes for a patient, it happens the day they get the dosing or maybe the day after it goes away, it comes back when you

reintroduce the drug, but sometimes it's more persistent, and if that's the case, it requires a little bit more legwork. I would just check to see if it's cardiac in nature or pulmonary in nature. Venous thrombosis is a risk at higher doses of carfilzomib, some swelling can happen, and all the proteasome inhibitors can increase your risk of developing herpes zoster, so you need to be on some sort of prophylaxis for that. So preventing some of these adverse events – carfilzomib does have a rare side effect of causing a hypersensitivity event during the infusion. I've really never seen it in my career, and I think it's because we always give steroids prior to the carfilzomib dosing to help prevent that from happening. IV hydration is required during the first cycle, really only the first cycle alone, to help prevent tumor lysis syndrome, which is very rare in myeloma. You do need to do VTE prophylaxis at the higher dosing for carfilzomib, zoster prophylaxis as well with an antiviral, be it acyclovir or valacyclovir, check the blood counts, and of course, we always do a baseline cardiac evaluation before we give patients carfilzomib. It can rarely drop the EF or cause other cardiac issues, so it's important to get a base. We typically, at Memorial Sloan Kettering, get a baseline echocardiogram on all our patients before we start, or at least have one fresh within the year. If they are reporting shortness of breath, we do repeat that echocardiogram to make sure there isn't any change in their cardiac status.

Now ixazomib, we know it's a pill, it can cause a lot of stomach upset, nausea, constipation, or diarrhea. It can cause thrombocytopenia around Day 15. We can see peripheral neuropathy with ixazomib but not to the frequency and the extent that we see with bortezomib. We can see some swelling, and again zoster

reactivation with this drug. So monitor your patient's blood counts, make sure they're on prophylaxis for zoster, make sure you're doing some sort of risk assessment for VTE prophylaxis when you're giving it in combination with lenalidomide and dex, and a little anecdote, we like to premedicate our patients with steroids when they take this drug. Remember, dexamethasone is an antiemetic as well, so we always tell our patients to take their dexamethasone in the morning with food, and then take the ixazomib later in the day, either an hour before you eat or 2 hours after; it's a little bit well tolerated when you do that.

So the monoclonal antibodies, we have daratumumab, which is an anti-CD38 monoclonal antibody. It works in several different ways. It has direct on-tumor activity, immunomodulatory actions and also direct cell death, and then elotuzumab is an anti-SLAMF7 monoclonal antibody – it's like alphabet soup – anti-SLAMF7 monoclonal antibody that basically works by targeting SLAMF7 that's located on the myeloma cells and natural killer cells. So elotuzumab can actually help tag the myeloma cell by making it more apparent for the natural killer cells for apoptosis. So daratumumab, it's given in combination with len-dex at first relapse, bortezomib and dexamethasone at first relapse, in combination with pomalidomide if patients have received two or more prior lines of therapy, and it can also be given in the monotherapy setting, which we may do. A lot of the time we use that in the elderly population, and it's given 16 mg/kg, and it's dosed weekly in the beginning because we're kind of overloading those receptors. For the first two cycles, it's given weekly, so you tell your patients to hold on tight because then it goes every other week after that, and then the home

stretch, they get it once a month thereafter in combination with bortezomib and dexamethasone, and it's given weekly, then it goes to every 3 weeks, then it goes to monthly. So daratumumab, probably the number-one side effect we see with this drug is it can cause infusion-related reactions. It's a long day that first day for your patient, so make sure you educate your patient that they may be in your center for about upwards of 10 hours. The infusion-related reaction initially in the early tries was happening about 50/50 – about 50% of the time – but we got smart. We figured out that most of these reactions are really eliciting kind of a bronchospasm. So if we premedicated our patients with montelukast, we saw much less infusion-related reactions. So I can tell you standards of care at Memorial, we give our patients montelukast prior to dosing even the day before and then also the same day as their first day of the cycle. It can interfere with serologic testing. CD38 is a weekly express on red blood cells, so it can make it really difficult to figure out your patient's blood type, so it's very important to get a baseline type and cross on your patient before you start daratumumab, and you must notify your blood bank that your patient is on daratumumab. It takes several months for this problem to clear even when they're done with the drug – upwards of 6 months. It can cause some neutropenia and thrombocytopenia, and remember, it's a monoclonal antibody. What's myeloma? An overproduction of a monoclonal antibody. So it can make it difficult to figure out if your patient has a complete response because when we're doing that serum protein electrophoresis that Dr. Richter so beautifully outlined in that illustration, you can actually pick up the daratumumab as a monoclonal antibody; it's an abnormal protein on your

SPEP. So how do you figure that out? Well, we're becoming a little bit more sophisticated and able to tease out if that monoclonal antibody is truly the daratumumab or your patient's actual abnormal clone. Daratumumab is an IgG kappa monoclonal antibody, so if your person has a different clonality, it's pretty easy to recognize that it's probably the drug you're picking up and not their different clone, but we have a lot more work to do to tease that out. And then they also can increase your risk of developing shingles, so patients need to be on prophylaxis. So how do we prevent this? We've got to premedicate our patients before we start this drug with your usual stuff, so they need a little bit of corticosteroids, they need acetaminophen, they need an H1 and an H2 antagonist, and also montelukast is highly recommended. The risk of an infusion-related reaction can be delayed, even up to 48 hours after getting the drug, so you do have to do post-dosing of corticosteroids 48 hours the day after and 2 days after as well. Antiviral prophylaxis to prevent shingles reactivation, monitor the blood counts, and please let your blood bank know that this patient is going to be starting on daratumumab.

Now we're trying to figure out how to make daratumumab a little bit more of a friendlier drug to give because it's a long day that first day, and then subsequent dosing can be about 3 or 4 hours, and I don't know about you, but a lot of my patients still need to work, and it's hard to tie them to a chair for that long. So there's some studies coming down the pike; this was just published, it was the phase 3 COLUMBA trial looking at subcutaneous daratumumab. Now, it's not a shot, it's a subcutaneous infusion going over 5 minutes. So this trial was

looking at over 500 patients who had relapsed/refractory myeloma. They got a flat dosing of 1800 mg of the subcutaneous dose of dara versus the standard 18 mg/kg IV, and the primary endpoint was progression-free survival, and patients – the overall response rate for IV dara was about 37%. The overall response rate for the subq dara was 41.1%. And when we looked at the progression-free survival, we see 6.1 months for the IV dara, 5.6 months for subq, but when we looked at 6-month time point for the overall survival, we saw 87.5% for the subq versus 83% for the IV dara; and why that is, it's because the earlier trials, the earlier phase 1 trials, were actually looking at the mean concentration of the subcutaneous drug versus the IV drug, and the mean concentration of the daratumumab in the subcutaneous formulation was much higher in the weekly dosing versus dara. So I think that's why we're seeing higher numbers for subq versus the standard IV. And when we look to see infusion-related reactions, we saw much less, of course, in the subcutaneous group, 12.7% versus 34.5%, so over a third for the IV group. And when we look at the median time for onset, we know with daratumumab, it's usually the body's first introduction to the drug, people can have a reaction, or when you bump up the rate, so about maybe within 30 minutes or an hour and a half, but with the subcutaneous formulation, the reaction is a little bit delayed. So about 3-1/2 hours later, we can see a reaction to the subcutaneous formulation. When we look also at injection site reactions, really rare with the subcutaneous formulation, about 7%, and we saw much less of that bronchospasm and chills with the subcutaneous formulation versus the IV. And interestingly enough, a lot of the patients in the subcutaneous

arm had a lot of high-risk cytogenetics, so it was interesting that you see kind of better response rates in the subcutaneous group because they were comparably a sicker population.

Now elotuzumab is an anti-SLAMF7 monoclonal antibody. It stimulates the immune system, those natural killer cells. It's indicated to be in combination with lenalidomide and pomalidomide, and it's dosed 10 mg/kg weekly for the first two cycles with len, and then it goes every other week; but for pomalidomide, we actually can increase the dose to 20 mg/kg, and we can actually give it monthly after those first couple of cycles. So adverse events? Much less infusion-related reactions with elotuzumab, only 3 to 10%. Infections? There's an increased risk of infections with elotuzumab. Interestingly enough, we do see higher secondary primary malignancy with elotuzumab, although rare, single digits. We can see a little bit of transaminitis as well. Again, it's a monoclonal antibody, so we can detect it on that SPEP. It can cause zoster reactivation and a little bit of myelosuppression. So again, premedicate your patients. Patients do need to take steroids prior to dosing of the elotuzumab, antiviral prophylaxis, infection precautions, and monitoring their labs.

So we look at all the drugs that have been approved, their regimens, including lenalidomide. We've done a lot better than some of those earlier slides I showed you in terms overall response and overall survival. So we have the ASPIRE trial looking at carfilzomib in combination with len-dex; the TOURMALINE study looking at ixazomib with len-dex; the POLLUX trial looking at daratumumab with lenalidomide; and the ELOQUENT trial looking at

elotuzumab, lenalidomide, and dexamethasone. So these overall response rates are really promising, close to 80% if not over 90% with the daratumumab combination. Not only are we getting high overall response rates, we're seeing really deep responses, which is amazing. This is a relapsed/refractory setting. So we're seeing really deep durable responses with these combinations. We're seeing really high progression-free survivals, and we're now counting not just months, we're looking at close to years for these patients, and some of the overall survival time points haven't even been reached in some of these studies.

When we look at the proteasome inhibitor–based studies that were approved, so we have the ENDEAVOR trial, that was a head-to-head comparison of a first-generation proteasome inhibitor versus a second-generation proteasome inhibitor, so carfilzomib versus bortezomib. The CASTOR trial was looking at daratumumab with bortezomib. The PANORAMA study, which is the panobinostat with bortezomib. The elotuzumab early study looking at it with bortezomib, and the carfilzomib/dexamethasone study. So some of those are a little bit earlier phase studies, so smaller numbers. Again, really high overall response rates for these patients in the relapse setting, and we're actually achieving CRs or VGPRs, which is more than a 90% reduction in that monoclonal burden. We're seeing PFSs at a year or more. Overall survival, again for a lot of these studies, haven't been reached, so we still are monitoring, just seeing how patients are doing.

I want to talk to you a little bit about the daratumumab-carfilzomib-dexamethasone study because a lot of these studies that were looking at

lenalidomide didn't really include patients who were refractory to lenalidomide or heavily pretreated with lenalidomide. So this study was looking at a patient population, looking at daratumumab in combination with a second-generation proteasome inhibitor carfilzomib in that special population. So we're looking at patients who have relapsed disease, one to three prior lines before, they have never seen carfilzomib, preserved ejection fraction and blood counts and performance status. So how it was given in this trial, is you actually were allowed to option for split dosing of the daratumumab, so not trapped in that chair for 10 hours, but you had the option of getting daratumumab split over 2 days at 8 mg/kg, or you could get it kind of in the 1-day dosing fashion, which is the standard, given on the usual cycle. Carfilzomib was given at that loading dose at 20 mg/kg on Day 1 and then escalated to once weekly dosing at 70 mg/m^2, and dexamethasone was once weekly. And the endpoints? Well, they were looking at safety and tolerability, but they also wanted to see overall response rates, overall survival, and also they were trying to see if patients achieved MRD negativity. So the majority of patients actually got split dosing in this trial, and then only 10 patients actually got the standard single dosing. When we look at the response rates, very impressive response rates, so we're seeing 84% overall response rate. We see deep and durable responses, and we saw that the splitting of the dosing of the daratumumab was very feasible and a nice option for patients. When we tease it out looking at patients who are actually refractory to lenalidomide, we were still seeing really good response rates, so close to 80% response rates, VGPRs close to 70%. When we looked at those patients who

were not refractory to lenalidomide but just exposed, those patients benefited the most, and 90% overall response rate and getting a complete response, which is basically no evidence of that monoclonal protein, close to 40%. When we look at the PFS, we can see at 12 months all treated was about 74%, the len-exposed patients but not refractory, again got the highest at 87%. So really, really good response rates for this drug combination, and this combination will most likely be approved I think sometime next year is when we'll be able to be giving this combination to our patients. Common adverse events? We did see some hematologic toxicity. We're well acquainted with managing a lot of this stuff, and some of it was actually grade 3-4, most commonly thrombocytopenia, which we know is reported with both daratumumab and carfilzomib. And nonhematologic toxicity, the most common we saw was a little bit of nausea, increased rates of upper respiratory infections, but most of the nonhematologic toxicities were low grade.

Now some of the pomalidomide-based studies that we have, a lot of these are kind of smaller studies, so early-phase studies. Pom-dex, you know that was approved many, many years ago. Bortezomib in combination with pomalidomide and dex, that's a large phase 3 trial we'll be talking about shortly. Carfilzomib with pom-dex, daratumumab with pom-dex is approved. Ixazomib with pom-dex and elotuzumab with pom-dex is also approved. And a lot of these patients were really heavily pretreated, and again, we're seeing really good response rates, high overall response rates for these patients and deep responses; we're achieving VGPRs for these patients. Progression-free survival is a little bit –

we're seeing a little bit under a year for some of these patients and overall response rates not being reached for a lot of these trials.

So I'm going to talk a little bit about the ELOQUENT 3 study because this was just approved last year, elotuzumab being given in combination with pomalidomide and dex. So this trial had about 117 patients in it, and these patients had two or more prior lines of therapy, which is typically the case when you give pomalidomide. The patients have to have seen two prior lines of therapy. They have to be refractory to their last therapy or relapsed/refractory to lenalidomide and proteasome inhibitors. So again, an important patient population to look at as we're using lenalidomide in the maintenance population a lot more and more. We're seeing a lot of patients becoming really refractory to lenalidomide. Dosing typically as, you know, elotuzumab 10 mg/kg; pomalidomide at 4 mg; dexamethasone at 40 mg, and the primary endpoint was progression-free survival. Response rates? We're seeing again high response rates in this heavily pretreated population, so 53% overall response rate for the triplet combination, the doublet at 26%, and again, more durable responses to higher VGPRs and complete responses and intrusion complete responses. Interestingly enough in terms of mortality rates, we see higher mortality rates with the doublet versus the triplet, and when we look at progression-free survival for the triplet combination, 10.25 months versus pom-dex, which is a little bit under 5 months, which equates to a 46% risk in reduction of death or progression of disease with the triplet combination. Some adverse events that we see, it was pretty equal between the two groups. Most commonly, cytopenia is what we saw,

and infection is what we saw most commonly. Serious adverse events were pretty equal between both arms, but we did see a lot more people needing to discontinue a drug with a doublet versus a triplet, which is a little bit confounding. You would think that people wouldn't better tolerate a triple combination versus a doublet, but I think the reason why a lot of people with treatment discontinuation is because their disease wasn't as well controlled in the doublet versus the triplet. Infusion-related reactions, we see very rarely with the elotuzumab group, and really none of the mortality rates were considered to be related to the drugs.

Now the OPTIMISMM trial, so this combination, pomalidomide with bortezomib and dexamethasone, will likely be approved come probably mid next year. So this was a big phase 3 trial, a randomized multicenter trial. The primary endpoint was progression-free survival, and this was looking at pomalidomide and bortezomib and dex on a 21-day cycle. So pomalidomide was given for 14 days, bortezomib was given twice a week, dexamethasone weekly, 2 weeks on, 1 week off, and was comparing it to bortezomib and dexamethasone alone. When we look at the response rates, really high response rates, so 82.2% for the triplet arm versus the doublet arm was 50%, and again, we're getting very deep responses, high VGPRs, high complete responses, even stringent complete responses. This is really crucial. Remember, these are relapsed/refractory patients, and some of them are really heavily pretreated, so it's really impressive to get these kinds of rates in this patient population. Progression-free survival? When we look, the median treatment duration was close to 9 months in the triplet arm versus only 5 months with bortezomib; and when we look at the 12-month

PFS, close to 50%, a year and a half 36% for the triplet arm versus only 32%, and 22% for bortezomib and dex. And when we look at those patients who are kind of earlier in their disease trajectory, they've only got one prior line of therapy, we're seeing higher progression-free survival rates at 12 months and 18 months. Grade 3-4 treatment adverse events: We see a lot of myelosuppression with the triplet arm versus a doublet arm, and in terms of nonhematologic, we do see significantly more infections with the triplet arm versus the doublet, but all the other nontreatment adverse events, again, sort of in the single digits.

I'm going to turn it over to Dr. Richter to talk a little bit about some of the alkylators that we're using, panobinostat, our newly approved selinexor, and also transplantation.

DR. JOSHUA RICHTER Yes, I get to talk about alkylators because as Amy said, I'm old and I use old drugs. Actually just to kind of dovetail, I'm going to steal one of your slides for a moment. The reason, if you look at every myeloma trial that compares three drugs to two drugs, and the three drug wins out almost all the time. The three-drug regimen will always have more upper respiratory tract infections, pneumonias, edema, cataracts; and a lot of this actually has to do with more dexamethasone or steroid exposure. So if you have Regimen A where people are on 4.6 months, and Regimen B they're on for 10 months, that's 10 months more of steroids, and we take for granted that that actually leads to increased infections as well, so that's part of the problem there. Yes, old drugs like me, alkylators, they're not as fancy and cool as CAR Ts and bifunctionals and garbage disposal proteasome inhibitors. The way I like to think

about this is finding a nice clock and throwing a monkey wrench in it. Alkylators, basically just part of the classical chemotherapy approach, interrupt the way that all cells replicate.

So one of the drugs that we don't use as much in the United States, this is used a lot more in Germany, is bendamustine. Bendamustine is a bit of an older drug. It's kind of got features of an alkylator and then features of a purine analog, so it's kinda like you mix fludarabine and cyclophosphamide a little bit. So the good thing about bendamustine is that there actually is good response with the drug. It isn't the greatest of all time. I tend to use this drug in people who have myeloma that likes to behave like lymphoma. I think that, you know, they've called diseases like lupus “the great imitator” where really myeloma is the great imitator. We all have those patients that are plasma cell leukemics, and they're behaving like leukemics. We have the myeloma patients who just have lytic bone disease. We have those patients who have these huge soft tissue plasmacytomas, and they behave more like myelomas, and I feel anecdotally that, you know, giving them big doses of alkylators like melphalan, like cyclophosphamide, like bendamustine, really help that type of bulky disease, and again, we look at the median PFS and OS, these are short months. Now first of all, these are people who are very heavily pretreated, and as Amy put out, people who are penta-refractory have a median overall survival of 1.7 to about 3 months. I think the big reason to consider a lot of these drugs is if you look across the last 11 years, we've had 11 drugs. But this is accelerating. There are four drugs or therapies slated to be approved next year, including several others that might be

approved and new combinations, so this is a great bridge to the next great thing, maybe a bridge to a transplant, a bridge to a CAR T, a bridge to a clinical trial. So bendamustine is actually a good tool in your toolbox for patients who have had the standard lenalidomide, bortezomib, but even selinexor.

So classical chemo generally doesn't work very well in myeloma, and the reason is classical chemo was invented around World War II, and a bunch of really smart people got together and said, "All right, well, what is cancer?" And cancer is cells that divide rapidly without listening to our body's cues that they should go commit suicide. So they developed a whole bunch of chemotherapy like nitrogen mustard and 5-FU and drugs like this that interfere with the way that cells divide, and the reason that you have the classical toxicities of hair loss and nausea is because those are the cells that divide rapidly in the body. Well, myeloma doesn't divide rapidly. If you think about your Burkitt lymphomas that divide really, really fast, and we call them the Ki-67, that replicate of index of about 100%. Myeloma is about 1%. If it's really crazy, it's like 3%. So given boluses of chemotherapy don't do anything, but if you stretch out the infusion of chemo, you catch cells that are quiescent and then start to replicate and then the classical chemo is able to kill them. And one of the foundations for this is a regimen called DCEP, which is a 96-hour continuous infusion of dexamethasone, cyclophosphamide, etoposide and cisplatin. And again, this is a really great bridge to something. The other realm that we use this in is chemo mobilization for patients that we're trying to move forward with upfront transplant but either have a suboptimal response to induction or progress on induction. This is a great two-

for-one where you hit them with the 96-hour infusion, it debulks them, and upon hematologic recovery, you collect their stem cells. And there's a number of variations of this; you can add and omit in it. So you can go from DCEP to DT-PACE, which not only adds the IMiD but also adds the anthracycline doxorubicin. You can go the next level and add a proteasome inhibitor and give them VDT-PACE, and VDT-PACE really became popular a number of years ago in a regimen called Total Therapy. Now probably many of you in the room haven't heard of Total Therapy, and for those of you who have, you can laugh because you know about it. So one of the giants that we get to stand on the previous work is a man by the name of Bart Barlogie, who had come from MD Anderson to go to the University of Arkansas and decided to attack myeloma much in the same way we treat younger patients with ALL, which is we throw everything at them, and he created this concept of Total Therapy. And basically these people had VDT-PACE, got collected, then thal-dex in the middle, then they got another VDT-PACE, then they got a transplant, thal-dex, another transplant, 3 years of thal-dex, I mean, this was like, literally was absolutely everything, and at the time people were making fun of him for this, though if you look at their data, it's still better than almost any other data, and now it's kind of coming the other way, so now that we had len-dex and VRD, and now there are studies of quadruplets, we're doing the exact same thing, just with more novel therapies. So again, this regimen was really great early on for people that you need a response this minute, and there's some patients where you can wait a week or three or a few

months to get their response, but if you need response immediately, this stuff is great.

Histone deacetylase inhibitors are FDA approved, although not heavily utilized in myeloma. In fact, they were voted down at the ODAC, and then were subsequently approved much in the same way that it happened to selinexor. And when they got approved, they were approved with two black box warnings: diarrhea, which many of the patients will report is worse than what they get with the transplant, and as a result, cardiac abnormalities, and much of this is because if you poop that much, you poop out all of your magnesium and potassium and have dysrhythmias. But histone deacetylase inhibitors, they synergize well with a lot of our other drugs, and this was really based off of the PANORAMA study, which combined panobinostat with bortezomib, really great combination, although, you know, the response rates were not that great, a little bit tough to tolerate. One of the downsides of this trial was that the panobinostat was given back-to-back weeks, and we now know that if you give it every other week, you have far less toxicity in terms of diarrhea, so with subsequent studies, we combine it with drugs like carfilzomib or pomalidomide, and patients tolerated it way better; they were able to stay on therapy quite long. And again, it's one of those things that nowadays I think everyone in this room, just like me, you sit down with a patient when they come in, and you give them VRD or some mild variation of that, and then they progress, and you give them something with pom, and something with dara, and something with car, and in the old days, you'd get through one or two regimens and the patients would succumb to their disease.

Now you can gave patients who blow through all the drugs, walk into your office completely fine, saying, "What's next?" and we're telling them, "Nothing." And, unfortunately, that's true for a lot of people, but I don't think this drug comes to the top of mind very often, so as you start running through the classic combinations of dara and pom and car, really important to remember panobinostat.

So selinexor or the new kid on the block, was approved July 3. It is a selective inhibitor of nuclear export; it's actually kinda cool. So we have these mechanisms of apoptosis where your body makes cancer, and the body says, "Ah, cancer, go kill yourself." And the cell says, "Absolutely." And commits suicide, apoptosis, and has this whole mechanism of targeted events that lead to cell death. Well, what cancer cells do is they kind of say, "No, I'm going to get around this." So there are these little holes in the nucleus, and what the cancer cell does is it kicks out part of that pathway, things like I kappa B or NF kappa B. So you have a pathway of 10 things in the nucleus that need to happen for the cell to die, and the cancer cell kicks out one or two of them, and the cell can't die. What selinexor does is it selectively inhibits the nuclear export of these compounds out. So instead of being kicked out, they're trapped inside, and the cell is forced to undergo apoptosis. Why is this important? This actually is something that we see in almost every cancer. So this has the potential to become the next checkpoint inhibitor in cancer because this works everywhere. The next approval is going to be in lymphoma. It works in GYN malignancies. The drug crosses the blood-brain barrier, so it's being studied in GBM. So this

drug actually will start to have far reaching ramifications. In fact, there's a veterinary version that is curing dog lymphoma. Yeah, for those of you following the dog lymphoma literature. So the pivotal STORM trial—STORM is Selinexor and the Treatment of Relapsed Myeloma—gave selinexor 80 mg twice weekly along with dexamethasone, looked at all the standard outcomes, and when you look at it with an overall response rate of 26%, you know, your first reaction is going to be like, "Well, you know, that's not that great." But if you think about the recent approvals and their overall response rates, so daratumumab was approved as a single agent, 29%; carfilzomib, 23.2%; pomalidomide, 28%. So the current single agent approval rates are around 25 to 30%. The really interesting thing about this was there were patients in the STORM trial who actually had prior CAR Ts. Next year, we expect the approval of CAR T therapy, and the good thing about this is we already have some data to say what should we do when they relapse from a CAR T because CAR Ts aren't curative just yet. In terms of AEs, a lot of this myelosuppressive. The biggest tropism is for platelets. So patients really tank their blood counts, especially in the twice weekly dose. So we're really starting to use a lot of the TPO mimetic strokes like romiplostim and eltrombopag, and going to very high doses rather quickly. The other thing is asthenia. There also happens to be probably a homology with sodium channels, so if you see hyponatremia, grade 3 is like 20%. Now part of this has to do with a flaw in the CTCAE, and the CTCAE for hyponatremia, grade 1 is lower limit of normal to 130, there is no grade 2, and grade 3 is 129 down to like 120. Most of the patients on trial came in asymptomatic at 129, 128, and

we'd have to hold drugs, so it's not usually a severe thing, but the standard rules apply: go home and eat a bag of chips, so we recommend heavily salted foods. Thrombocytopenia is a big one, and really starting to use TPO mimetics and cranking up the dose pretty quick, so using romiplostim at doses like 10 ng, or using eltrombopag at around 100 mg.

STOMP is the next generation. This is a nice little basket trial. We're combining selinexor with all the other classic drugs, so selinexor with lenalidomide, with pom, with bortezomib, with car, with dara, and you see across the board, it's weekly dosing, and the drug is tolerated far, far better at a weekly dosing. So the way that most of us use it now is we use it in triplets, but instead of giving 80 twice a week, the majority of the combos are with 100 mg once a week. It comes in a little blister pack, and we're talking about it a little bit earlier, this drug is $22,000.00 a month, so it's quite expensive, and there's actually several ways to order it. You can order it at 80 twice weekly, you can order it once a week. You can order all the different versions, but if you order the 80 twice weekly, you get the most pills per copay, and then you can tell the patient to use as many as you direct them. So we treat a lot of patients here, and here we're starting to see in triplet combos overall response rates of 63%, PFS of 9 months, so we're starting to get really better outcomes when we combine it earlier and in triplet therapy, and if we look at the combination with seli and dara, we see overall response rates that are in the mid to high 70s, so this is really with all drugs, same thing with dara. Dara as a single agent was 29%. When you put it in second line with len, it's a 93% overall response rate. Selinexor is once

weekly, with dara moving further up, it's getting to those high numbers as well. This is really important because quads are moving to the upfront therapy. So if you have someone upfront who's getting daratumumab, bortezomib, lenalidomide, and dex, and then they progress, and you put them on car-pom-dex, where do you go next? And you have to start considering drugs like selinexor.

So transplants? Very, very common. And autologous transplants are not really transplants, they're stem cell rescues. We take advantage of a dose response curve with melphalan, and we just give people really high doses that just wipe out their marrow, and then we give them back some stem cells to rescue their marrow, still part of standard upfront therapy, though it's becoming more and more controversial who needs a transplant. Because if you're able to get those really deep responses with our novel therapies, maybe we can avoid it, maybe just save this for salvage.

Allogeneic transplants, very controversial. Most sites don't do them. They are associated with a higher mortality, so depending upon all the factors, you know, in a high-volume auto transplant center, the risk of mortality is less than half of 1%. For all transplants, the mortality can be 10 to 20%, which is a much, much different number, so really, a very select group of patients going through allogeneic transplants.

And syngeneic, identical twin transplants, now few people may know this, but Amy and I are actually identical twins, and I'm glad that people finally recognized that. But it turns out that syngeneic transplants actually have the best

outcomes ever in myeloma. You get really the best of both worlds, you get no graft-versus-host disease because it's really kinda like the same cells, but there are subtle antigen differences when you do a twin transplant that may actually get you a little bit of that graft-versus-myeloma we hypothesize. So it's one of those things, if you actually have a twin, we very much recommend these because given the small data, people do much, much better. And I think I turn it back over to you.

AMY PIERRE All right, so we talked a little bit about all the current therapeutics that are approved for multiple myeloma. We are fortunate in the last 5 to 10 years that we've had a lot of new agents approved in all different combinations, which is fantastic, but also it elicits a little bit of confusion, right? What agents do we use when for our patients? We know that treating myeloma is best by taking a little bit from Column A, a little bit from Column B, a little bit from Column C, attacking the myeloma in many different ways, different mechanisms of action, but what do we use when? So how do we choose therapies for our patients? How do we really figure it out in terms of appropriate selecting of the drug combination and sequencing?

So we have a couple of things that we think about: (1) Is this a real relapse? Is this a true relapse? Because sometimes after patients get an autologous stem cell transplant, you can see these little oligoclonal bands that pop up on the SPEP and they're immunofixation. It's not really relapsed disease, it's just kind of immune reconstitution. The immune system is just kind of reregulating itself, and it will go away after a couple of months usually. So that's

not a true relapse; don't rush and treat your patient. But when someone does relapse, there's a couple of things we have to consider, some disease-related factors and some treatment-related factors. So disease-related factors, is this a significant biochemical relapse? Are they completely asymptomatic, but their M-spike has jumped up? Or is this a really symptomatic aggressive presentation? They have new bony disease, renal failure. We gotta use a regimen that has a quick overall response rate, and a deep response. Also the whole concept of fit versus frail. We've kind of thrown age out the window, right? Age is nothing but a number. We've kind of thrown it out the window, and we're really using that get-up-and-go test. Is the patient fit or frail? Can they handle this regimen or not? So looking at performance data is when we're considering what agents to choose, and also what was their duration of response to the private therapy? Did they get a lot of years out of that drug? A lot of months out of it? Is it possible if it's in their first relapse, they had a remission and the disease has come back, and they had a response for a long time. Maybe we could actually recycle that old regimen back if they didn't have a lot of toxicities associated with it. And also, risk stratification, right? As Dr. Richter talked about, we have that whole concept of clonal evolution, and as the disease peters on over the years, you acquire more and more high-risk cytogenetic features. Almost everybody towards the end of their disease trajectory with myeloma has acquired deletion 17p, and there's some drugs coming out in the market that actually target some of these molecular abnormalities. So it's important to know what their risk stratification is when it's coming upon relapse. And then some treatment-related factors, so what

were the prior therapies? Did they respond well to them? Did they have a lot of toxicity to them? Are they relapsed, or are they actually refractory to those prior agents? And also, what are their comorbidities? If someone has poor cardiac function or cardiac status, or poor kidneys, all of that is really important to consider when you're selecting the agents. And mode of administration is becoming more and more important to our patients. Some people can't get to the cancer center all the time when we need them to, to get their visits and their drugs, so some patients may benefit from an all-oral regimen if appropriate. And, of course, we always have to consider the patient, right? This is not really a paternalistic or maternalistic atmosphere for medicine anymore. We really want more dynamic conversation with our patients and them participating in the decision making because it is kind of a two-part decision. So we can also think about the acronym TRAP, right? So Timing of therapy; Response to prior therapy; Aggressiveness of the relapse; Performance status – to help us figure out what agent and what drug combination is important for my particular myeloma patient sitting in front of me. Make sure it's individualized and tailored to that patient. Think about shared decision making. This is kind of a new model of care that we're doing in myeloma. It's basically listening to your patient, listing what their preferences are and what their goals are, and coming at a mutual decision about what agents are approved for them and their disease trajectory, and what's appropriate for them given their needs and their disease as well. So seek your patient's participation, help them explore the different options. If you look at the NCCN Clinical Practice Guidelines, there's a list of maybe 10 drug

combinations to give your patient at relapse. So it's really helpful to walk your patient through the different options so they can understand why you're recommending that regimen and hear what they have to say about it as well. Reach a decision together and evaluate the decision as a team.

So some takeaways, triplets are generally preferred over doublets. We really only give doublets to our patients who are on monotherapy for patients who are maybe elderly or have a lot of comorbidities, but we do know there is a role for quadruplets. In fact, daratumumab has been approved to be given in the newly diagnosed setting as a quadruplet regimen.

We have to do a risk-adapted treatment selection for a patient. Think about the side effect profile, think how the drug is administered. Can they tolerate it? Can they come to the cancer center? Are they frail? Are they fit? What was their prior response? How aggressive is their relapse? Are they symptomatic, or are we just seeing a slow gentle rise in that serum M-spike? And make sure you tailor your adverse event prevention and management to each individualized patient.

So let's do a case study. So let's talk about Debra. She's a 65-year-old female who is married, and she's working full time in finance in the city, and she presented 3 years ago with ISS stage II IgG lambda multiple myeloma. So her past medical history, she's got high blood pressure, but it's really well controlled with medications that she takes, and she did have some compression fractures when she first presented to you 3 years ago that was successfully treated, the pain was alleviated with kyphoplasty, and for her induction regimen 3 years ago,

she got four cycles of VRd, so bortezomib with lenalidomide and dexamethasone. She got a VGPR, so that's more than 90% reduction in that monoclonal burden. She got an autologous stem cell transplant, and she got a CR, and when we actually checked her bone marrow post-transplant, she was MRD-negative, which is fantastic. She got 2 years of bone-modifying therapy with zoledronic acid, and now she's on lenalidomide maintenance therapy, and she's presenting to your office. So we take a look at her laboratory studies. Her blood counts look pretty good on her lenalidomide regimen of maintenance. Her chemistries look really good. But when we take a look at her paraprotein panel now, we see reappearance of that M-spike that was gone, and now it's back, over 1 gm. So is this a true relapse? When we look at her clonality, her immunofixation shows it's truly an IgG lambda that we're picking up, which is consistent with her original clone, so this is smelling like a real relapse. How is she feeling? Is this a symptomatic relapse? Well, she tells you, "You know what? I'm actually feeling okay. I'm tired, but I work a lot in the city, full time. I still have a little bit of diarrhea related to lenalidomide, but it's now well controlled with the colesevelam." So we know that a lot of studies have shown, and we're actually doing a clinical trial at Memorial Sloan Kettering, that the lenalidomide-associated diarrhea is really due to bile acid malabsorption, and colesevelam is a bile acid sequestrant, and so we've been using a lot of it for patients who are not really getting response with Imodium for the lenalidomide diarrhea. We're giving them colesevelam, and we're seeing a much better control in their diarrhea. She tells you that her back pain that really was kind of gone after she had the kyphoplasty

is now starting to bother her again, but she's been working a lot in the garden this past summer, so she thinks maybe she's kind of overdone it, but as a myeloma professional, your antennas are going off. This patient has back pain, right? So we do a PET scan, and we basically restage her. So we do a PET scan, and we see she's got new lesions in her spine at L1 and L2. We repeat her bone marrow, we see that now she's got 20% of those abnormal plasma cells in the bone marrow. She still has her translocation (11;14), but she's now acquired due to clonal evolution that translocation (4;14), which is kind of a high-risk signature, a poor prognostic sign. So what can we give Debra? It's her first relapse, right? So the world is her oyster. There's several different drug combinations we can give her. Some of them we know she's a little bit too early for, some of those pomalidomide-based regimens. She's gotta see a little bit more therapy before she can get that, but the world really is her oyster. There's a lot to pick from, so how do we figure this out? Let's do a little bit more legwork. Is this a true relapse? Absolutely. She's got new lesions in her spine. We repeated her bone marrow, 20% plasma cells. So it's a true relapse. She's pretty fit, right? She's working full time, she's gardening. Her duration of response is pretty good. She got a good 3 years out of her initial first line of therapy, and remember her induction regimen of VRd plus the autologous stem cell transplant plus the lenalidomide maintenance is all one-line therapy. So this is her first relapse. She's only had one prior line. When we do her risk stratification, she's acquired that high-risk translocation (4;14), and when we look at treatment-related factors, she is relapsed. She's not really refractory to lenalidomide, but she's seen a lot of

lenalidomide, right? I don't know if we really want to bring that back again, and she's progressed on maintenance. Toxicity from prior therapy? Not really. She doesn't really have any toxicities from her induction regimen. Mode of administration? IV, oral; we'll talk to her about what we think is good. We'll figure out what some of her preferences are when we work this out. So we do a little bit more legwork, we see that she's really symptomatic. She's got that high-risk feature. We do an MRI of her lumbar spine to get a closer look about her back pain. We don't see a compression fracture, but we do see a little bit of epidural disease, so now we're thinking maybe a radiation oncology consult for her. She tells you, "Look, I've been doing a lot of research online, and now I know you guys can give me all oral therapy. I don't have to come in for all those shots anymore; I'm not interested in that. I'm busy, I gotta work. I want an all oral regimen." So let's sit down and talk about this, Debra. So she's not really refractory to lenalidomide, but she's seen a lot of it, so it's possible to give her IRd, but I don't know if I really want to do that, to be honest with you. She's got that high-risk feature. She's never progressed on bortezomib. She's actually never been exposed to pomalidomide. Proteasome inhibitors we do know kinda help overcome that translocation (4;14) signature, so I think we want to give her a proteasome inhibitor as part of her treatment regimen, but we talk to her about all the options, right? We talk to her about dara, we talk to her about carfilzomib, bortezomib, IRd, a clinical trial, we talk to her about elo. We tell her a little bit about what we know in terms of the overall response rates, what the patients look like in all those trials, and we tell her we'd rather use a triplet combination

versus a doublet because she's fit, and so we actually end up choosing bortezomib with pomalidomide and dex because of the OPTIMISMM study, and we know she'll have a good response, and they actually had patients on that trial at first relapse, so we know those patients did really well on it. So what do we need to think about Debra on OPTIMISMM? Well, we need to make sure she's taking her oral pills because pomalidomide is oral, and we have to ensure the REMS compliance. We need to monitor her blood counts because the most common toxicity is related to the trial for neutropenia and also infection. We saw a little bit of that on that trial. We do need to give her some VTE prophylaxis with the pomalidomide and figure out what her risk stratification is. If we use that SAVED score model, she's pretty low risk, right? So probably just a baby aspirin is sufficient for her. Zoster prophylaxis because the bortezomib can increase the shingles reactivation, and the traditional side effects we see with both of these agents we need to monitor for. Give her a radiation oncology consult and bring back that bone-modifying agent. So she comes back to you on the first day of her second cycle. She says she's doing fine, she's still working. She's noticed a little bit of easy bruising, but no spontaneous bleeding, no peripheral neuropathy, which is great. She had an awesome weekend. Her little grandson came to visit her. He coughed and sneezed all over her, so now she's got a sore throat, she's got a runny nose, she's coughing. She felt a little bit cold yesterday, but she didn't have a fever, and you look at her vital signs, she's coming into your clinic, she's afebrile. So what are you going to do with Debra? Well, let's take a look at her labs. Whoa, she is neutropenic, right? That was probably the most common

side effect we saw with that trial, and she's sick. She's probably infected. She's got some thrombocytopenia as well. Her platelet count has dropped to 50 from 219. Her chemistries have come a little bit out of whack. We now see renal insufficiency that's so common with our myeloma patients, right? They get a cold, they get sick, they come in your office. Their creatinine is bumped up because they're not really drinking well, and we know that kidneys are so susceptible to injury for our myeloma patients. But, her M-spike has come down, right? 1.16 not to 0.57, that's more than a 50% reduction, so she's responding to therapy. She just, unfortunately, has a cold and has a little bit of toxicity from therapy. So we've got some myelosuppression. We see acute renal insufficiency. She's achieved the PR, a partial response. She's probably got some sort of viral syndrome. So what are we going to do as advanced practitioners? Well, we're going to culture her up. We're going to give her IV fluids to help that bump in her creatinine. We're going to hold her anticoagulation because her platelet count is 50. Anything 50 or below, we hold anticoagulation until the platelet count has recovered. We're going to delay her cycle and give her a week to kind of get over this, give her a little bit of maybe filgrastim, maybe support her with some antibiotics, she is neutropenic; supportive medications for her symptoms, and strongly consider if she comes back to you and she's still myelosuppressive, because sometimes this myelosuppression can be just related to the drugs and the infection itself, if she comes back to you again, and she's still myelosuppressed after holding the drug, you might need to consider a dose reduction for her.

So let's talk a little bit about what it is to be an advanced practitioner at Memorial Sloan Kettering, it's a very sunny day there with flowers. It's a lot colder there now, I must tell you. So what we're doing at Memorial Sloan Kettering, we're really a part of a multidisciplinary team, which is great. Our opinions are really valued. We're seen as part of the team, you know, we do a lot of the new consults, we're the first face that you see, which is really nice for patients, very reassuring. We get to sit down and spend time with them, kind of go over the disease, and then leave a little bit of work for the doctors when they come in the room, but it's nice that we're the first smiling face that they see. At Memorial Sloan Kettering, we do have APP grand rounds that are done every month; it's broadcasted through all the Memorial Sloan Kettering Centers, even the regional sites. We do have a newsletter too to talk about, what's going on for APPs in Memorial Sloan Kettering and some announcements as well. We also have a journal club, and it's online, so literature that's pertinent to advanced practice we talk about every month; there's a discussion board for it. We have the NP council. I, myself, serve on the regional subcommittee for our site. There's also mentorship programs too for advanced practitioners who are new to the game, very new NPs; you can mentor them as well. And we're developing a clinical ladder right now, which is really great to reward those NPs who are really seasoned or do a lot of work to improve APPs as a whole, either doing presentations or publications, so we're trying to do a lot for our APPs at Memorial.

Now at Memorial, we're doing a lot for multiple myeloma as well. We do see specialists at every disease level, so your radiation oncologist is a myeloma specialist, your stem cell transplant doctor is a myeloma specialist, and we're trying to define myeloma early, right? Why wait for that CRAB criteria for diagnosis? We're trying to figure out and define the disease at a much earlier stage, so looking at smoldering, looking at MGUS, and we're looking at how myeloma is different, right? It's multiple myeloma, the disease isn't the same for everybody. Everybody responds differently, so we're focusing on, and we're developing kind of clinical assays to look at the heterogeneity and also trying to figure out how to define MRD negativity even better than what we do. Right now, it's 10^{-6}, but can we even do better than that? And wellness, we're focusing on a lot of wellness. We have a lot of clinical trials looking at biomarker monitoring, people wearing those kind of devices. We're looking at like sleep patterns because none of our patients can sleep on dexamethasone. We're looking at activity as well, and we even have our colesevelam trial, and we're looking at a lot of different targeted therapies for relapse to myeloma. So, you know, targeting BCMA, you know, the antibody-drug conjugates, by specific monoclonals, CAR T, so we're looking at a lot of different therapies coming down the pipeline.

So when we look back at Debra 3 years later, she did really well on OPTIMISMM but, of course, she relapsed, and we gave her dara, we gave her carfilzomib, but she keeps relapsing, we keep seeing the evidence of that clonal evolution. So she comes to your clinic because she wants to know what to do next. So we really push clinical trials pretty much at every level at Memorial

Sloan Kettering, and if you go to our website, you can just go right to our website on multiple myeloma, go to the clinical trial website, type in relapse, and bam, about 80 different trials come out for the treatment of relapsed/refractory multiple myeloma. Let's talk about what's going on at Mount Sinai.

DR. JOSHUA RICHTER So if they have 80 trials on myeloma, we have 83; I'm just going to be quite honest. So in general, I couldn't agree more with the statement about clinical trials, and there was a statement once that was put out to say that until we have 100% cure for 100% of patients, we need aggressive clinical trial activity, and one of the benefits, you know, people often think about clinical trials in the very end stage. I actually am a big fan of early stage, and the reason why is nowadays, we've heard Nurse Practitioner Pierre – if you're going to call me Dr. Richter instead of Josh, I'll call you Nurse Practitioner Pierre – talk about all the different drugs we have, that we have proven benefit. If you put somebody in early relapse on a new trial, and it does not work, you have a laundry list now of proven therapies to help them, but if they benefit from that, and they stay on that, you still have those in your back pocket and new ones that come along the way, so early involvement in clinical trials is extremely important. So at Mount Sinai, again, we always have more trials and better trials than at Sloan Kettering; it's part of how we do things.

And so one of the things we have is an induction of dara RVD for transplant-ineligible patients, and it's important because we know that transplants do really well, but we also know now that people who get those deep responses, the MRD negatives, probably do just as well with or without transplant. So giving

a dose just of the RVD lite that a lot of us give in clinic, giving that plus dara, if we get high rates of MRD negativity, we may obviate the need for transplant for these patients, or they may get those same benefits even if they're older or frailer. Maintenance, you know, kind of the standard out there is lenalidomide, but we still don't do as well for the high risk, so we have a maintenance study comparing len versus dara-len.

CAR Ts are very big. bb2121, which will likely be approved next year, the J&J Legend CAR T, a whole bunch of others. Bifunctionals, I think they're going to be very big in myeloma because they're off-the-shelf products. CAR Ts are great, but for the moment, they're not off the shelf. You've gotta collect the patient, you've gotta manufacture the cells, you gotta bridge them, so if you have a patient with myeloma that shows up in renal failure today, your CAR T is over a month away, bifunctionals being off the shelf are great drugs. So BCMA-targeted, CD38, and a newer target called GPRC5D, which is going to be the next generation of therapies.

A few novel targets, so ONC201, which really looks at some of these p53 patients. AMG 397, which is an MCL-1 inhibitor, which actually combines very well with BCL-2 inhibitors, we'll talk about in a minute. The cell mods, CC-220, iberdomide, coming soon to a clinic near you, probably the most active IMiD out there, and we're really excited to get this into the clinic, also next-generation CD38, so just as you guys have rituximab, and then there's also obinutuzumab and ofatumumab, the next generations. We have next-generation CD38s, TAK-079, SAR442085; the ADCs, the antibody-drug conjugates, so belantamab,

which is an antibody-drug conjugate targeting BCMA, will likely be approved next year, very active drug, working on symptom control, just like Sloan.

Mutational-driven therapies, this is a really great trial under the MMRC and MMRF called MyDRUG, which a patient who has functionally high-risk disease gets sequenced, and they get ixazomib, pomalidomide, and dex plus something that we know drives their disease. So there's a large number of patients with *BRAF* mutations in myeloma. So if you have a *BRAF* mutation, you get IPd plus a BRAF inhibitor. If you have a RAS, IPd plus a MEK inhibitor, ERK inhibitor, so on and so forth, so we're giving really personalized therapy, that thing we keep telling patients we're getting to but we're not quite there yet.

The other thing is we have a brilliant scientist by the name of Samir Parekh, who does whole-exome sequencing, RNAseq, basically finding out all those subclones, what those subclones look like and how to target them, so we've put people on crazy drugs. I got a text while we're here, I have a gentleman that we've done this on that we found out that he has a RAS mutation, which is great, there's no RAS mutations approved for myeloma, but trametinib is out there and approved in a variety of other places. So he's on daratumumab, thalidomide and trametinib. The reality is that we can start thinking outside the box when we have this type of evaluation.

So we're going to talk a little bit about some of the novel therapeutic agents, and some of these are actually likely to be approved within the next year, so it's very exciting. So venetoclax is an oral BCL-2 inhibitor. As many of you know who treat anything other than myeloma, this drug is already approved in

acute myeloid leukemia and lymphomas. It's used everywhere. It's like drinking – it's going to be in the drinking water any day now. It's really great, and the interesting thing if you look on the left, if you work on drugs that get to MCL1 and BCL2 together, you really get some amazing responses, so there's several anti-MCL1 inhibitors in clinical trial. Hopefully, you'll use them soon, but drugs like carfilzomib and bortezomib really synergize well with venetoclax. The monotherapy has been extremely important, and again, the big thing about venetoclax is this it's actually personalized medicine. Venetoclax really works in two types of myeloma patients: those with (11;14) translocations and those who are highly expressers of BCL2. So if you look in the overall population, it's so-so; much better in t(11:14) than those without; really good in people who are high BCL2 expressers. The issue for the moment is there was a registration trial called the BELLINI trial, and the BELLINI trial randomized people to bortezomib-dex versus venetoclax bortezomib-dex, and there were more deaths in venetoclax bortezomib-dex arms, so the FDA put a hold on it, and they're going through data analysis and a whole bunch of other things, and hopefully we'll get this drug approved for myeloma in the next year. Again, for the people who do harbor (11;14) translocations or high BCL2, the response appears to be quick and quite durable, so as patients start to go through some of our standard therapies rather quickly, we repeat the marrow, and a lot of times, they'll say, "Well, why are we doing that? We know they have myeloma." And just exactly as Nurse Practitioner Pierre pointed out, that sometimes you acquire new mutations or you have a new dominant clone, so you may not have had an (11;14) in the

beginning, but now the dominant force is (11;14), and we should bring venetoclax in. Again, when we start combining with proteasome inhibitors because of their effect on MCL1, we see even higher rates of response, so here we see all patients at 68%, but some of the earlier relapses up to 89%, and again, these are quite durable responses. Venetoclax is an oral drug, which combines well, and as opposed to some other diseases like the lymphomas where you have to ramp up dosing because of a fear of flare, again, myeloma doesn't really turn over very fast, so you can start right ahead on the high doses, usually 400, in some rare cases, 800 daily. Duration of remission? Pretty decent for these heavily refractory patients. And again, anything we do with one drug, we have to do with another drug. The study of carfilzomib and venetoclax, a lot of this is being done under Dr. Stadtmauer, who is giving a talk here in the coming days; highly recommend seeing anything that Ed says; he's brilliant. And again, here, in all these patients who previously had the PIs and the IMiDs, the standard drugs we use all the time, overall response rates in the 80s, and again, even when you look at the double refractory, refractory to lenalidomide and bortezomib, still really high response rates. Again, these are small numbers, but unfortunately, we're not curing anyone, so we always have to think the next step.

Okay, they progressed on this, where do you go? And you start going through drugs rather quickly, really kinda thinking about using venetoclax for those two groups of patients. Iberdomide, also called CC-220, this is a CELMoD. In many ways, this is just the next generation of immunomodulatory drugs, so thalidomide, lenalidomide, and now iberdomide, and iberdomide appears to have

activity even in patients who are progressing beyond len and pom, and as many of our therapies, doublets, triplets, quadruplets, include IMiDs, and we know that provides a really great backbone for the patient, this is going to be the next step in backbone, so look for this drug soon. I think it still has a little bit of time before approval; I think it's 2021 or 2022, but it's going to be a mainstay of our therapy in the future. And again, to try to identify what the best combo is because just because a couple of cells in the lab tells you this combo is the best, or this one's not, the human being is a complex scenario, so we try all the combos to figure out what's best. We're running this trial now, and so far, the response rates are exactly, you know, where we're thinking about in the heavily refractory group of patients who are still hitting that 25 to 30-some odd percent response rate, very exciting as a new oral therapeutic option.

Melflufen is actually a drug that's flown a little bit under the radar, but I'm actually really excited about it. It is a lipophilic peptide conjugated alkylator, or basically, it's melphalan on steroids, and the really great thing about it is, you know, as we get more and more novel therapies, fewer and fewer people get alkylators as part of their therapy. You know, I think in the day and age when we used to give CyBorD – cyclophosphamide, lenalidomide, dex, upfront – we do a lot more VRd now. And a lot of people used to get a transplant, but as we're finding less and less of a need in some patients, we're using less and less of it. So you can think about people who run through a lot of the classic drugs; you get dara-VRd upfront, you get dara-pom-dex or, sorry, car-pom-dex in the first relapse. You are now triple-class refractory, penta-refractory, having never seen

an alkylator. The benefit of melflufen is it's basically a monthly infusion of a version of melphalan. So it's a once-a-month infusion; it's an alkylator; many of these patients are alkylator naive. It's well tolerated. It does have some myelotoxicity, but again, with a lot of our therapies being aggressive in terms of dosing, once weekly, twice weekly, to ask a multiply relapsed myeloma patient to come into clinic once a week, it's a lot, but once-a-month infusion is very nice, and this will hopefully be approved next year. So immunotherapy, this is like the buzz word for all cancer. We're trying to cast off our history of poisons, we're now ushering the new wave of immune modulation and immunotherapy, and I hate to break it, every drug in myeloma is immunotherapy. Dexamethasone is immunotherapy. So it's not just your pembrolizumabs and durvalumabs; when you're killing immune cells, they're all immunotherapy.

And there's some big targets that we know about, and BCMA is really one of those big ones that we're really trying to hit. BCMA is B-cell maturation antigen; it's on all myeloma cells. So what other antigens have we looked at? A whole host of other ones. And again, how do we decide which ones are worthwhile? Well, are they expressed on myeloma cells or not? And then what other tissues are they expressed on? So it's very interesting when you start looking into this.

So GPRC5D is a new antibody that we're studying. It's great. It's on all myeloma cells. It's also on skin cells. And for those of you have given capecitabine, that hand-foot syndrome, we get that with this drug in the clinic because it just so happens that target is on the hands, so now we're starting to

give those packets with Udderly Smooth and the Bag Balm and all this stuff, and some of the younger docs and nurses are looking at me like I'm crazy because yes, I'm old, but it's really interesting when you think about where these other antigens are expressed, you get other toxicities.

Bispecific antibodies, really great. So we have one of these drugs approved, blinatumomab , which is approved in ALL, and it's bifunctional. It's got a CD3 and CD19, so it grabs onto the CD19 cancer cell, grabs onto the CD3 cell, and puts them together and has your immune system kill it. We have several of these drugs in clinical trials, none of them yet approved for myeloma. But again, it's off the shelf, which means you don't have to manufacture anything, you don't have to delay therapy, and it's a parenteral drug, so when drugs like this are approved and someone comes in on a Monday in renal failure, you can give this to them on Monday or Tuesday. One of the ones we're looking at is GBR 1342. This is an anti-CD38/-CD3, and at least in some of our preclinical models, it actually has more activity than daratumumab, probably from the fact you're getting enhanced immune activation.

ADCs, antibody-drug conjugates, these drugs have been used for many years with varying success. Brentuximab vedotin is a drug a lot of you probably use, which is an ADC. Gemtuzumab ozogamicin is another ADC that's used in myeloid malignancies. And basically, these are just in my mind really cool things. You have some kind of link, and an antibody you attach to anything, in this case that has BCMA, and then you inject poison; sounds like a really cool drug. The one that's really on the verge of being approved within the next probably 6 to 12

months is of course 2857916. Actually, it has a cooler name, it's now belantamab. So the reality is there are several anti-BCMA therapies that are headed towards clinic. Obviously, bb2121, which is a CAR T, and belantamab, which is an ADC.

Now in my mind, the way that we currently conceptualize myeloma, transplant eligible or transplant ineligible, is kind of a colloquialism for how we're thinking about people—the younger, fitter, get transplants; the older, frailer don't—and that mode of thinking is evolving for things like anti-BCMA therapies, do you need at CAR T or not? I have to admit I think that's the only small version. I really do think the bifunctionals and ADCs are the future; they're off-the-shelf products, which is really what you need for myeloma treatment, and there's several reasons: (1) Myeloma can progress fast out of nowhere, you don't have time to manufacture; and the other reality is that it doesn't matter that this week I saw 40 patients with myeloma, it doesn't matter. The average heme-onc group sees 0 to 10 myeloma cases a year, but 70 to 80% of all myelomas are treated out in the community. That's a large percentage of people, and they're not ready to get CAR Ts, and a lot of those patients are older, frailer, they can't travel for CAR Ts. So only about 30% of people in the United States that are transplanted who are transplant eligible. So really I think the forefront of BCMA therapy is going to be belantamab, it's an excellent drug, and what we found is there's only one real toxicity, is a little bit of keratopathy. But what we've actually found, it's so potent that it works. You give a dose of it, and let's say you have to hold it because of the keratopathy that you need to improve, by the time that resolves,

the patient is still in remission, and that wasn't the case for a lot of other drugs that we have. So the fact it's dosed appropriately, we can get around the keratopathy, it's extremely potent, and it's really going to usher in a new realm for treating patients. As we can see, there's some people here who have absolutely amazing responses, and we've treated many of these patients and had great success with it. You know, one of the things to remember is the unique toxicity. So as this drug gets into the clinic, it's good to have an ophthalmologist to work with you to make sure you're able to keep patients on the drug as much as possible. And again, the ocular toxicity is really the thing you have to look out for, but this is easily gotten around. Most of this is self-limited, you hold the drug, it goes away; so really not concerned in the long run.

So CAR Ts, we gotta talk about CAR Ts because it's the cool kid on the block – chimeric antigen receptor T cells. And this is how they work. But really what you're doing is you're engineering T cells to go fight the tumor cells, and it's kind of exciting. Two of these have already been approved, tisagenlecleucel and axicabtagene ciloleucel, in leukemia and lymphoma, and now we're looking to approve these in myeloma. Next year, we're probably going to see the approval of bb2121, but there are a lot of things that come around after you give CAR Ts that you have to think about, and the biggest one is cytokine release syndrome. So this is not to be taken lightly, and essentially for those of you have given high-dose IL-2 to treat diseases like melanoma and renal cell carcinoma, do you remember? Did you guys used to do that? I did it too, and I think the other people still laugh at me for being old. For those of you who haven't, you give high-dose

cytokine therapy on the floor, then the patient looks like they're septic, they have a blood pressure of nothing over nothing, the floor staff yells at everyone else saying this patient needs to go to the ICU, and then everyone says, "No, they're fine with a blood pressure of 70, they look great." And it flips everyone out, and you kind of support them through that period of quasi-shock, and then they get better, and their disease is in remission, but those cytokines we see when you infuse the T cells in the patients, these cytokines come up, IL-1, IL-6, and these patients will have high, high fevers, low blood pressures, they look like they're going into septic shock, and it's a major issue to deal with. How do we assess our patients at the bedside? We have different scoring systems, the CARTOX-10, the ICE. One of the biggest things we have patients do is actually write a sentence every day, and it's interesting to see that when this starts to come on with neurologic toxicity, they don't write it very well. We follow them very closely. So once we give CAR Ts, how do we deal with it? So there's several ways to deal with CRS. The first one is to give tocilizumab, which is an anti–IL-6, and you can give tocilizumab, or siltuximab is another anti–IL-6. If that doesn't work, you can always give anakinra, which is anti–IL-1. If that doesn't work, or you have neurotoxicity, you actually give steroids, and you give steroids because steroids penetrate the blood-brain barrier, so if you have any neurotoxicity, you give dexamethasone 10 q6, but again, you want to be careful about giving dexamethasone too early. Remember that dex kills lymphocytes; that's why steroids are in all lymphoma regimens, steroids are in all myeloma regimens, and when you give steroids and check the CBC the next day, you see that the white

count is up and it's all neutrophils, and the lymphocytes are down. If you give somebody a CAR T-cell product and you give them steroids, you've killed the CAR T. So if you give it too early, you'll actually negate all the anti-tumor effect. And it's still quite controversial. Do you need persistence of the CAR T to control the disease, or does it just do what it does, and it doesn't matter if it leaves the system? Very controversial, but the other way, if they have neurotox or refractory CRS, you have to give them dex, and if that fails, and we've actually had a few patients get to this point, well, you can give them chemotherapy that kills T cells, so we've given people drugs like cyclophosphamide to stop aggressive CRS. Post-CAR T, what do you have to look for? Pancytopenia. One of the big issues with CAR T patients after they get discharged is prolonged cytopenias. There's actually some anecdotal evidence that the more disease burden they had going in correlates to the duration of cytopenias after, so the person that had 80 or 90% plasma cells in the bone marrow before the CAR T, expect them to be cytopenic for 2 months or more; hypogammaglobulinemia, so making sure these patients get regular IVIG, especially as we're heading into cold and flu season; and infections. So besides from the regular vaccines and the regular HSV prophylaxis, CMV PCR should be checked monthly almost in the same way that we deal with our post-allogeneic patients.

Current trials? Dozens of them, even more, targeting all different types of things. The majority target BCMA. Dr. Stadtmauer, who is going to give a lecture on this a little bit later, is actually doing something really cool. At least, ask him; he thinks it's really cool. He actually gives two CAR Ts at the same time to some

patients. He gives them a CD19 CAR T and a CD38 CAR T at the same time; he's treated about a dozen patients. So again, we're still trying to figure out a lot of these answers, and a lot of the things that we don't know is what's the right cell dose? What's the right target? What's the right patient? What's the right lymphodepletion? All of these really key questions are not going to be answered before the FDA approves this stuff, but there are ongoing questions to help perfect the technology.

So b2121, the closest one to being approved, and this is the general scheme. You screen patients, you leukapherese them much in the same way that we collect stem cells early on for transplant, but this time instead of collecting CD34-positive stem cells, we collect T cells, then you send it out for manufacturing, and in the meantime, you give them bridging chemo. This is some type of chemotherapy to hold the disease under control so they don't explode with some type of problem before the infusion. Then you need to create immunologic space, right? Because patients have their T-cell repertoire, and if you infuse some jacked up T cells, it's only a voice in the crowd. You need to make that the dominant T-cell force. So first, we lymphodeplete by giving them cyclophosphamide and fludarabine, and then we put in the T cells in an infusion, and then they essentially stay in the hospital for about 2 weeks, although they now have protocols for outpatient CAR Ts. Overall the response rates have been very high, especially when you get above a certain cell dose. The other interesting thing is tumor response seems to be relatively independent of BCMA expression. It's always our first thought for these studies that only the people with

high BCMA levels are going to work for a BCMA target, but almost like every other thing we've seen, you know, in the old days we actually thought in order to give hormone therapy for breast cancer, you have to have +4 ER/PR, and even if you have 1%, you'll still probably respond. Same thing for rituximab, you have to have everything, CD30-positive, even if it's not, so there's off-target activity, but overall, even if you have any myeloma, even with low expression of BCMA, you're likely to respond. The median progression for your survival is 11.8 months, but in those who responded, 17.6 months, and these patients had a median of seven lines of prior therapy, so this is that group that has a median overall survival of 1.7 to 3 months, so when you look at these numbers, it's actually quite impressive in that group. Again, you'll see you really need to have a good cell dose to get it. Nobody knows what that ideal cell dose is; there's probably at least 150 to 300 million. CRS was generally low grade and manageable, and obviously for high-grade CRS, we attack it with drugs like toci, steroids, anakinra, but for grade 1/grade 2, you have to think about it because we're thinking about this a lot like graft-versus-host disease, you know, sometimes we think a little bit of GVH is probably a good thing, just enough to give you a good graft-versus-tumor, and the same argument is being made here. There's a little bit of CRS, meaning you're getting that immune activation to control the cancer, so we're trying to let a couple of these patients float. Obviously, not the altered patient with the 105 temp and 70 palp, but the patient who is otherwise fine, has a little bit of a headache, a fever of 101 but has a 10/10 CARTOX, we should just let it slide.

The other thing to really think about is Foundation Medicine for the heavily advanced patient, and a lot of you out there who treat other diseases, I know I treat one disease, but for people who treat multiple diseases, you use a lot of Foundation Medicine, especially in those metastatic diseases of unknown primary where you're trying to figure out where did this come from, some lung lesion? Foundation Medicine has this amazing list of genes, and I know it's unreadable, but the point is they look for everything, and it spits out several really important pieces of information, and this is commercially available. We see it on our bone marrows. It gives us biomarker findings and genomic findings, so genomic findings is easy. If you have a myeloma that's driven by one of these genetic abnormalities, there are drugs that exist outside of the myeloma world to use. So *BRAF* is classically thought of as a melanoma driver. Well, about 10 to 15% of myeloma is *BRAF* driven, and about 15% of myelomas is *RAS* driven, and yes, even *BRCA* driven. Actually, although we think about *BRCA* as increasing the rates of ovarian and breast cancer, patients with *BRCA* mutations have higher rates of myeloma. So using drugs like CDK inhibitors and PARP inhibitors are things we use in myeloma, so combining these drugs, BRAF inhibitors, MTOR inhibitors, other drugs actually get to the driver of the cancer itself. The other thing you get is biomarker findings, and you see something here called tumor mutational burden. So one of the things that's in every cancer right now is checkpoint inhibition; nivolumab, pembrolizumab, atezolizumab, blah, blah, blah-mumab, all the different blah-mumabs, and they're great, and they work everywhere, and they cure people, except myeloma, there is still an FDA

kind of no-no on it, but it turns out that people with high mutational burdens respond well to checkpoint inhibitors, so there was approval for checkpoint inhibitors a few years ago, any MSI-unstable tumor, you can use these drugs. The same thing is kinda true of myeloma. So if you have someone who has blown through everything, and they have a very high mutational burden, we consider giving them checkpoint inhibition because, you know, risk/benefit is actually something else that we can do.

So am I supposed to talk about this one? Or am I – oh, yes, I am, sorry. Novel therapeutic takeaways. So there's a really lot that we're doing right now, and this is a screenshot I took a couple days ago. Look at the number of active trials in myeloma, and it's only around 3,000 right now. So the field is extremely crowded, and there's a lot of drugs in the pipeline, so we're really hopeful about the future and therapies we have, especially belantamab, I mean, we just really can't wait to get that into the clinic. Understand the mechanisms of action, and it's really important for emergent therapies. I think a lot of clinics that treat all different diseases, there's a hesitancy to incorporate a new drug in your pocket. You never wanna be the person to give blah drug and forget – ah, I didn't give the zoster prophylaxis, and they got shingles; I didn't give them PCP prophylaxis, and they got PCP – so incorporating new drugs is complex, but you want to make sure you're on top of it to monitor things and get them the most time on therapy. CRS is a really big thing, and we don't just see this in CAR Ts, we see this in bifunctionals as well. So most of our current bifunctional trials require a few-day admission in the hospital to make sure they don't develop CRS, but it

can happen. And we do have issues when we affect the immune system. When we overactivate the immune system, you can get autoimmune disease. For CAR Ts, when we clear out immunologic space and your only T cells are CAR Ts, that means you don't have T cells fighting fungus, viruses, bacteria; these patients get those weird things. And again, if you clear out all T cells, it's kind of like thinking about an end-stage AIDS patient; those are the type of infections we can see in people post-CAR T. And again, really consider clinical trials. Like I said, early involvement. If you put someone on a trial in the first or second relapse, and they fail, you can give them dara, car, pom, seli, dex until your heart's content, and they will respond. So I think for the final takeaways, I'll pass it to Nurse Practitioner Pierre.

AMY PIERRE All right, so key takeaways from our talk today. Remember risk-adapted treatment selection for our patients, make sure you're thinking of the patient sitting in front of you, make sure it's individualized, tailor your adverse effect prevention and management, understand what's coming down the pipeline with the new novel agents that are approved. We're doing a lot of targeted therapy, which is great. And always consider clinical trials at every level for all your patients, not just when they're heavily pretreated, but even sometimes upfront at newly diagnosed patients because we have a lot of great stuff out on the market right now.

All right, time for some Q and A.

DR. JOSHUA RICHTER: Yes.

FEMALE So this is a million-dollar question that I need an answer to. So when you have treated your patient with first-line therapy for bone-modifying therapy monthly for 2 years and then we transition typically to every 3 months, and then they have a relapse/recurrent disease, and you go to your next line of therapy, you said that you retreat bone. What schedule do you use when you retreat after they've already had 2 years plus?

DR. JOSHUA RICHTER I think that's a really great question. There was a time where this wasn't an issue, when, you know, we talk about the old days of myeloma, when from diagnosis to death was 2 years; there was no such thing as too much. Now we know there is such a thing as too much, you can get brittle bones and other problems. I think for lack of guidance, I'd do it on a case-by-case basis, so I think several things: (1) As part of the relapse, did they have more bony disease? If they had more bony disease, I'd tend to be more aggressive and still give it every 3 months. If they don't relapse with it, I'd still maybe give it every 6. The other thing that I think is very important along these lines is bone densitometry. Women are so much better at this than men, that women tend to get regular bone densitometry, and myeloma doesn't always cause bone lesions by specific lesions but can cause general demineralization. So along the way, especially for the male patients who are not as good at this, we get regular bone densitometry to get an idea should we be giving it more, or should we be giving it less? I think the patient who is just on it over time, you go from 3 months to every 6 months, there is, again, not quite ready for prime time, there's a lab called an NTx or a CTx, N-telopeptide and C-telopeptide, which is a marker of bone

turnover, and we're trying to figure out exactly the answer to your question, which is when they relapse, if they have higher rates of bone turnover, should we be adding more or less? But for the most part, I tend not to push it; I tend to keep it every 3 months for people with lots of bony disease, a little bit less, go to every 6.

FEMALE Mm-hmm, thank you.

AMY PIERRE We'll take one more just because of time, and some of you may be registered for another program coming up, so we'll take one more question. The rest, I'll ask you to come up to the desk, but go ahead with the next question.

FEMALE Just a follow-up on the previous question, so if a patient has renal failure, GFR is less than 30, do you give denosumab?

DR. JOSHUA RICHTER Yeah, we both do. I think denosumab is a lot easier to give to those patients. The one caveat is that the lower the GFR, the higher the risk of hypocalcemia, so prior to administration, checking vitamin D levels, checking calcium levels, and what I always tell patients is that if we give it to you, and you develop perioral numbness, which could be a sign of hypocalcemia, I say most people have a bottle of Tums at home, pop a couple Tums because that's calcium carbonate as a quick way to help replenish it. But, yeah, you really gotta be diligent about vitamin D levels of renal insufficiency.

[END]