Slide 1

Dr. Harvey: Hello, and welcome to our webinar, "Making Sense of the New World of Myeloma Care: Pharmacy Perspectives on Novel Antibodies and BCMA CAR-T Cell Therapy." This is an independent, commercially supported symposium that's being held in conjunction with the Hematology/Oncology Pharmacy Association's (HOPA) 17th Annual Conference.

I'm Donald Harvey, I'll be one of your panelists today. I'm joined by Dr. Kathryn Maples and Dr. Tim Peterson. I want to thank the Medical Learning Institute, the accredited provider, and PeerView Institute for Medical Education, the educational partner, for providing this session.

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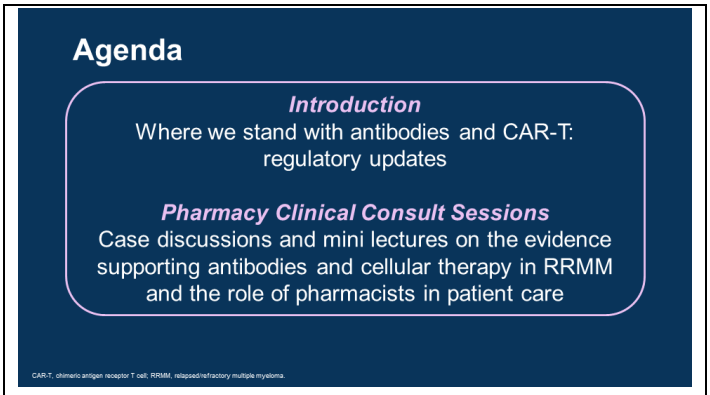

Today's agenda. We'll begin with a brief introduction of where we are currently with antibodies and CAR-T cell therapies and regulatory updates. Certainly, a lot's happened very recently, but also, a lot's happened over the last year and before, to really improve the therapy for patients with myeloma in various disease settings.

We have clinical consult sessions when we'll have case discussions and some lectures on the evidence that's out there for antibodies and drug conjugates, cellular therapy in patients with relapsed and refractory disease, and our roles as pharmacists in the overall patient care plan.

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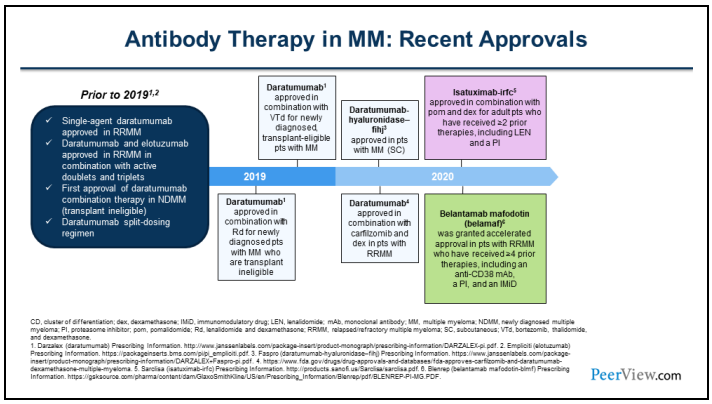

Let's start off with a brief history of antibody therapy in multiple myeloma. I'm often reminded that it's a little bit ironic that we have a disease that causes excessive antibody production, yet we hadn't had an antibody to treat it in many, many years until these approvals.

Prior to 2019, there was single-agent daratumumab. It was approved, and that certainly moved through the regulatory space quickly. Daratumumab and elotuzumab were approved in relapsed/refractory disease and began the expansion into doublets and triplets and other regimens for patients with advanced disease overall. But then daratumumab moved earlier on, and there were some other changes that happened in the space.

The first approval of therapy was in transplant-eligible patients for daratumumab. Then split dosing came into the role as well to help some of the operational challenges that might have been seen with daratumumab early on based on infusion reactions and as people gained experience with it.

It was approved in combination with lenalidomide and dexamethasone for newly diagnosed patients in 2019. It was also approved with bortezomib and thalidomide, again, in transplant-eligible newly diagnosed patients.

Then 2020 showed us a couple of changes as well in the landscape; the subcutaneous formulation of daratumumab was approved in combination with hyaluronidase, and then it was approved in combination with carfilzomib and dexamethasone, again, in patients with relapsed and refractory disease.

Subsequently, the second CD38 antibody, isatuximab, was approved, also in combination with pomalidomide and dexamethasone in patients with 2 or more prior lines. We also had the approval of belantamab mafodotin (belamaf), the antibody–drug conjugate targeting BCMA in patients with 4 or more prior therapies. These are all the antibody therapies that happened up to 2020.

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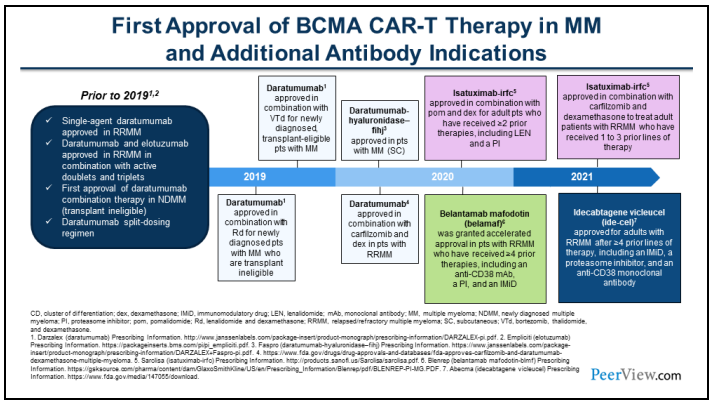

As we move forward into 2021, there have been additional approvals already—isatuximab in combination again with carfilzomib and dexamethasone in earlier lines of therapy, 1 to 3 prior lines. Finally, there is idecabtagene vicleucel—which has also been approved for adults with relapsed and refractory disease after 4 or more prior lines of therapy—as the first CAR-T cell therapy in this population.

We've had a lot of activity in the world of antibodies in myeloma, as well as cellular therapies, and today we're going to talk with you about what this means for pharmacists and overall patient care.

I'm happy to introduce Dr. Kathryn Maples, a colleague here at Emory University who was our clinical pharmacy specialist in myeloma, and have her begin the discussion of how you can integrate novel antibodies into myeloma. Kathryn?

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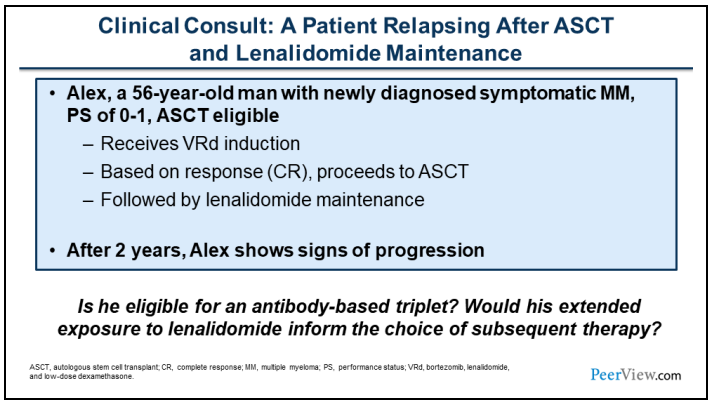

Dr. Maples: Thank you so much for that introduction, Dr. Harvey. I'd like to first start us out with a patient case. This is Alex, a 56-year-old man with newly diagnosed symptomatic myeloma with a performance status of 0 to 1 who is deemed to be transplant eligible.

He received VRd induction, and based upon his complete response, he proceeded to his autologous stem cell transplant, and then he was initiated on lenalidomide maintenance. After 2 years on this maintenance therapy, he's showing signs of progression and is in a need of a change in treatment.

A couple of things that jump out to me at first is that he is progressing at that 2-year mark, which is a little shorter than what we like to see. This may be an indication that he has high-risk cytogenetics or high-risk disease. We know that VRd induction, transplant maintenance, the median progression-free survival is closer to 5 years. We may need to keep in mind his disease cytogenetics when we think about the next line of treatment.

I'll open this up to my copanelists, Dr. Harvey and Dr. Peterson. What are your thoughts on this—is he eligible for an antibody-based triplet, and would his extended exposure to lenalidomide change anything for you in terms of what we should choose next for him?

Dr. Harvey: It's an interesting case. I'll start off, Tim, if that's all right. As you say, the early progression is concerning, so more aggressive treatment is probably part of it. It does bring you to the question. I'd be curious to hear your guys' thoughts on progressing on an immunomodulatory drug (IMiD), on lenalidomide, and what that means for subsequent IMiD therapy versus switching to another combination with

an antibody of a different class.

When thinking about high-risk disease, we think about proteasome inhibition with those cytogenetically defined high-risk categories. Certainly, if his performance status is still good after this, being more aggressive in a doublet or potentially even a triplet, as was stated here, makes a lot of sense to me. Tim?

Dr. Peterson: I would definitely agree. In the setting of what is clearly lenalidomide-refractory disease, I think we have seen activity in that context for pomalidomide-based therapies. We've started to see even more experience with daratumumab in combination with pomalidomide. We had some early-phase studies that were published a few years back, but we're getting more experience with that in early relapse.

We're also seeing daratumumab in combination with carfilzomib, which was the recent FDA approval that we had in that context, too. I think this patient definitely would be appropriate for antibody-based triplet therapy with a good performance status and aggressive relapse.

Honestly, depending on the clinical circumstances of his relapse, he may even require a bridge to outpatient meeting with something like infusional chemotherapy with DCEP, VTD-PACE, or something of that sort to get us to a situation where we can manage him appropriately outpatient.

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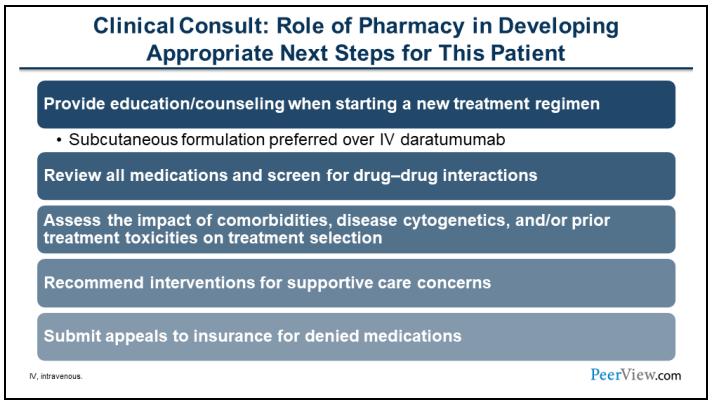

Dr. Maples: Yeah, absolutely, I agree with both of you. I think you both raise excellent points. Here are some things that we can consider as the role of the pharmacist for the next steps for this patient. First, we can always provide education and counseling when starting a new treatment regimen.

Subcutaneous daratumumab, which we're going to talk about a little bit more, has become the preferred daratumumab agent at many institutions. This may allow for quicker-starting therapy. I know many infusion centers have challenges finding that 8- to 10-hour chair for that lengthy IV infusion, and this subcutaneous formulation may afford the patient to get in for treatment much quicker.

We would want to review all of their concomitant medications and screen for any drug–drug interactions that we need to be aware of. We always want to think about the patient's comorbidities, disease cytogenetics, and prior treatment toxicities and how that may impact treatment selection.

For example, as Tim mentioned, we could potentially be thinking about a daratumumab/carfilzomib regimen here, but if the patient has concomitant heart failure, we may not want to do that for that patient. We should be thinking about patients as a whole.

Then we can be recommending any interventions for supportive care concerns. This can range from VTE prophylaxis, anti-infective prophylaxis, to bisphosphonate therapy. Lastly, the pharmacist may need to be involved with submitting appeals to insurance for any denied medications.

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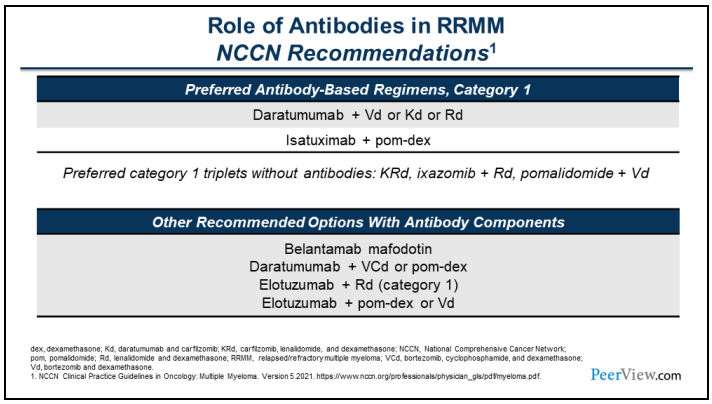

The NCCN guidelines have many different recommendations for our patients with relapsed/refractory myeloma, and there's no real consensus on which one should be selected. It is a very patient-specific decision, but some of our preferred antibody-based regimens that have a category 1 recommendation include daratumumab in combination with bortezomib or carfilzomib and dexamethasone, as far as our proteasome inhibitors.

We also have daratumumab plus lenalidomide and dexamethasone, which we would probably not want to consider for this patient; as we discussed, he would be deemed lenalidomide refractory. Then we also have our newer agent of isatuximab in combination with pomalidomide and dexamethasone.

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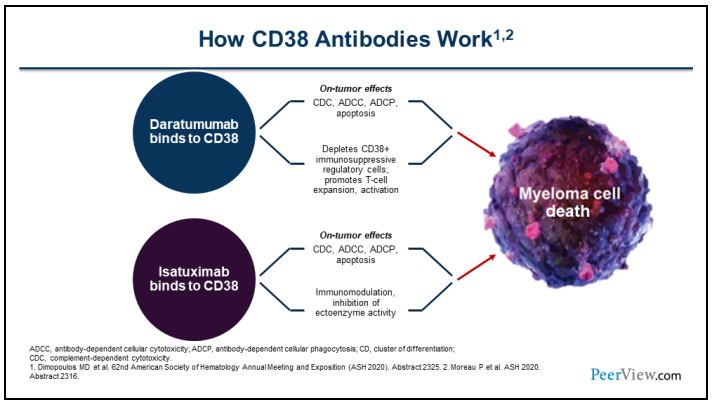

Since we've seen some growth in our CD38 role, I want to quickly review the mechanism of action for both of these agents. Daratumumab and isatuximab both bind to CD38 on the myeloma cells, and they have activity through the complement-dependent cytotoxicity, antibody-dependent cell-mediated toxicity, as well as antibody-dependent cellular phagocytosis.

Specifically with daratumumab, we see that it depletes CD38-positive immunosuppressive regulatory cells, as well as promotes T-cell expansion and activation. Isatuximab has some immunomodulatory effects as well as inhibition of ectoenzyme activity. All of this leads to myeloma cell death.

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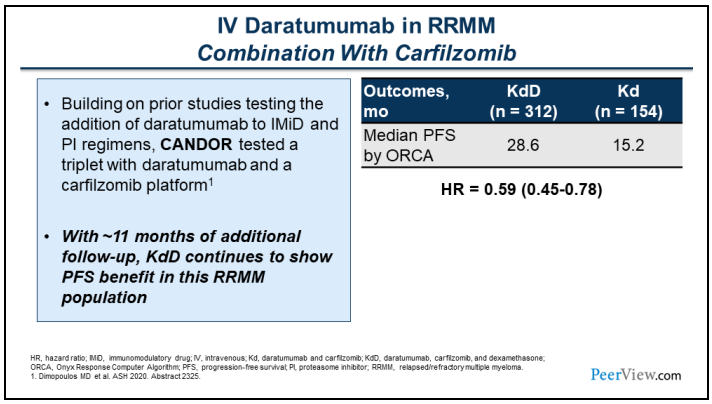

A review some of our more recent data with daratumumab in the relapsed setting. This builds upon our historical CASTOR and POLLUX data, daratumumab in combination with bortezomib and lenalidomide, which established daratumumab triplet therapy as a great option in relapsed myeloma.

We had this recent approval of daratumumab in combination with carfilzomib based on the phase 3 CANDOR trial, in which we saw that the median progression-free survival with daratumumab, carfilzomib, and dexamethasone was improved at close to 29 months versus 15 months with carfilzomib and dexamethasone alone.
With an additional 11-month follow-up, we continue to see that the daratumumab/carfilzomib/dexamethasone arm showed PFS benefits in this relapsed myeloma patient population. This could be an option for our patients who are in their initial relapse.

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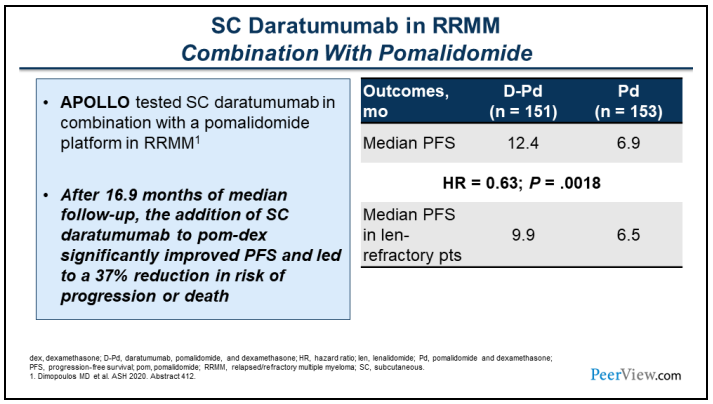

Also, at the American Society of Hematology (ASH) Annual Meeting and Exposition last December (2020), we had the APOLLO data presented. This was subcutaneous daratumumab in combination with pomalidomide and dexamethasone. One thing to keep in mind from this study is that these patients had a median of 2 prior lines of therapy, which is different from our CASTOR, POLLUX, and CANDOR populations, which were more than 1 prior line of therapy.

We saw that the combination of daratumumab/pomalidomide/dexamethasone improved the median progression-free survival to 12 months versus 6.9 months with pomalidomide/dexamethasone. We saw that this combination led to a 37% reduction in the risk of progression and death overall, and the benefit was maintained in those lenalidomide-refractory patients. I think our patient case, Alex, would be someone in whom we could consider using daratumumab/pomalidomide/dexamethasone for because he is lenalidomide refractory.

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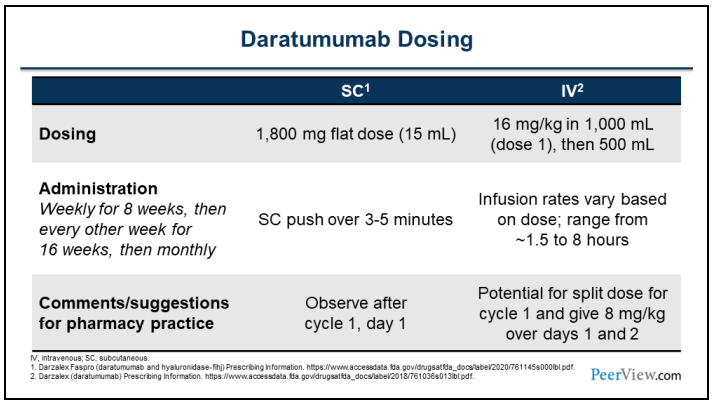

Daratumumab Dosing

	SC[1]	IV[2]
Dosing	1,800 mg flat dose (15 mL)	16 mg/kg in 1,000 mL (dose 1), then 500 mL
Administration *Weekly for 8 weeks, then every other week for 16 weeks, then monthly*	SC push over 3-5 minutes	Infusion rates vary based on dose; range from ~1.5 to 8 hours
Comments/suggestions for pharmacy practice	Observe after cycle 1, day 1	Potential for split dose for cycle 1 and give 8 mg/kg over days 1 and 2

IV, intravenous; SC, subcutaneous.
1. Darzalex Faspro (daratumumab and hyaluronidase-fihj) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761145s000lbl.pdf.
2. Darzalex (daratumumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761036s013lbl.pdf.

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When looking at our two different daratumumab agents and comparing the pros and cons of both of these products, as I mentioned, the subcutaneous product was approved in certain combinations. However, the NCCN guidelines have recommended that you can use these interchangeably. I know at my institution, we have preferentially used the subcutaneous route for all of our daratumumab regimens, with the biggest difference being the administration and the dosing.

We see that subcutaneous daratumumab has a flat dose of 1,800 mg, whereas IV daratumumab has the weight-based dosing. The administration listed here is our most common administration frequency that we see with daratumumab—weekly for 8 weeks, every other week for 4 months, and then monthly thereafter. The subcutaneous route is a push over 3 to 5 minutes, which is much shorter than our infusion rates, which range anywhere from 1.5 to 8 hours.

A clinical pearl and something to think about for pharmacy practice is that the observation period after subcutaneous daratumumab should be implemented after cycle 1, day 1. For those patients who have previously received IV medication and you're switching them over to the subcutaneous route, you really don't need to worry about monitoring those patients.

However, if they're initially starting out on cycle 1, day 1, then at our institution, we've implemented a 3.5-hour observation period. This came from the phase 3 COLUMBA trial; 3.5 hours was the median time to an infusion-related reaction, so that's why we chose that. But that may vary from institution to institution.

With IV daratumumab, you can consider doing split dose. That is helpful to make it a 4-hour infusion on 2 days rather than one long 8-hour infusion.

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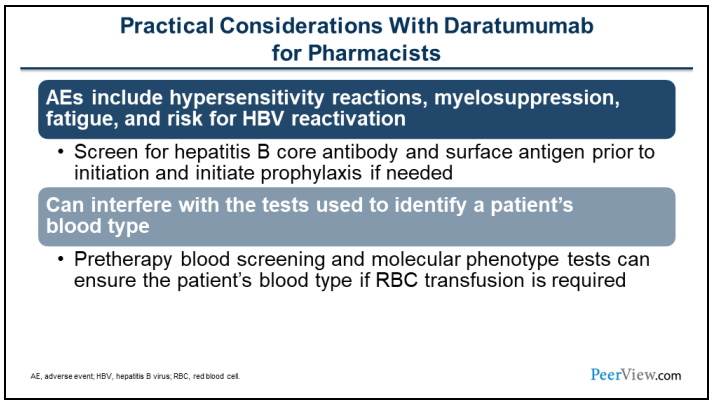

Some other practical considerations to think about—as we'll discuss, daratumumab and isatuximab have hypersensitivity reactions. We want to always monitor for myelosuppression and fatigue. Daratumumab does have a risk for hepatitis B reactivation, so screen for the hepatitis B core antibody and surface antigen prior to starting daratumumab and initiate prophylaxis if their hepatitis B core antibody is positive. We typically use entecavir, but you can also use tenofovir.

Daratumumab can interfere with tests that are used to identify patients' blood type, so you want to make sure that patients are getting their type and screen drawn prior to starting daratumumab so that the blood bank knows what blood type the patients are if they ever need a transfusion.

Also, daratumumab can interfere with myeloma screening because it is a human IgG kappa antibody and therefore it can show up on the SPEP and IFIX assays, so just keep that in mind.

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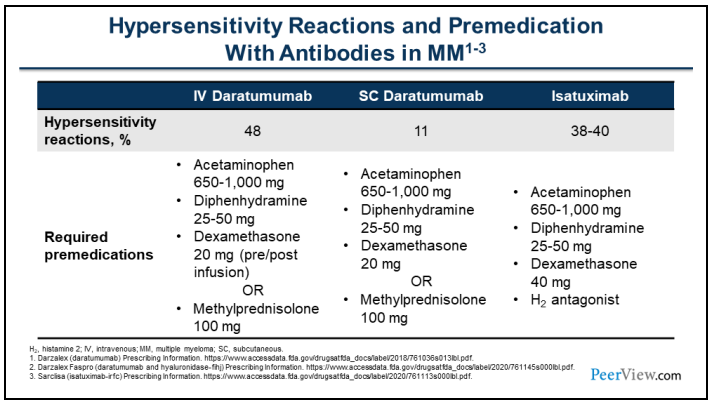

Let's look at hypersensitivity reactions with all three of our CD38 agent formulations—we have IV daratumumab, subcutaneous daratumumab, and isatuximab. Hypersensitivity was seen in around 48% of patients with IV daratumumab, 11% with subcutaneous daratumumab, and 38% to 40% with isatuximab. Most of these are typically grade 1/2, but it is something that we need to monitor for.

And you can see (slide 13), the premeds typically consist of acetaminophen, diphenhydramine, and a steroid component, with the H_2 agonist being added for isatuximab. One clinical pearl that we've implemented with our subcutaneous daratumumab is—we've noticed that many of our patients are self-driving, so they're coming to our facility and getting Tylenol and diphenhydramine, and then leaving 20-30 minutes later to drive home.

Once we've established that they're tolerating, we've removed that diphenhydramine component to avoid any sedation as they are driving home.

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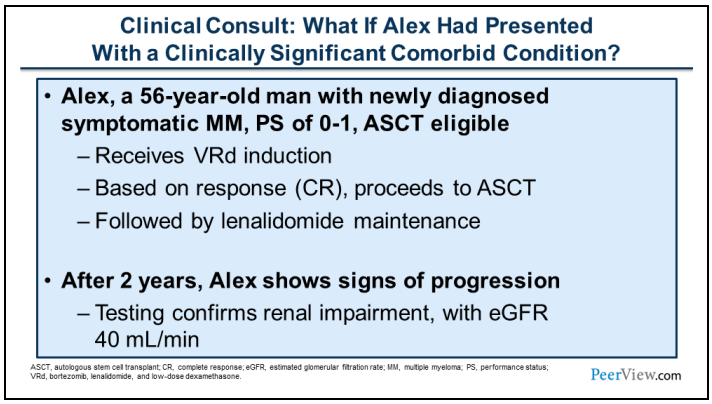

I want to circle back to our case briefly. Here we have the same patient progressing after 2 years on lenalidomide maintenance. However, this time he has some renal impairment, with a creatinine clearance of around 40 mL/min.

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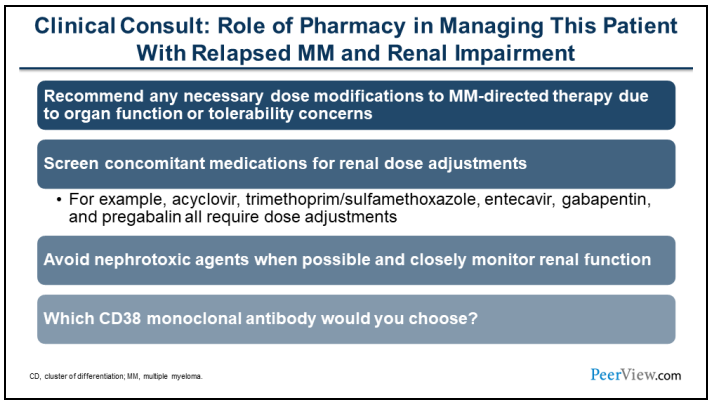

Here are some additional clinical concepts that we need to think about as pharmacists for this patient now that he has renal impairment. Look if there are any necessary dose modifications to both the myeloma-directed therapy as well as the supportive care medications.

Some of our supportive care meds that need dose modifications include acyclovir, entecavir, and any of the peripheral neuropathy medications. We want to avoid nephrotoxic agents when possible and keep a close eye on this patient's renal function moving forward.

I think one unique question that's been coming up now that we have multiple CD38 monoclonal antibodies to choose from is, would the fact that this patient has renal impairment impact your selection on what CD38 monoclonal antibody you would choose? I'll open this up to Donald and Tim to get their thoughts.

Dr. Harvey: When you look at it, you asked the question around antibodies, and I think about it from the geeky pharmacology perspective. Antibody and clearance, you know, it's all reticuloendothelial system. There's no direct impact of kidney function on clearance of an antibody. But then, that's the pharmacology side. The question then becomes, do you have clinical data with experience in these patients, and what does it look like?

So thinking about that from a CD38 antibody perspective, one might consider isatuximab as a preferred agent because there are data there. With either agent, I think, from a mechanistic perspective, you might make the argument, "Well, there's no real reason one should expect a reduction in clearance due to renal impairment." But then, where do the data land? Tim, what are your thoughts on that?

Dr. Peterson: I would definitely agree. I think in clinical practice, the preference is given to daratumumab just based on clinical experience. We've had probably 6 years or so since the FDA approval of daratumumab, so there has been a lot more experience with it.

However, as you were referring to, the data with regard to daratumumab use in moderate to severe renal dysfunction is primarily a small case series that is retrospective in nature. There's a paucity of data supporting daratumumab's use in that context.

I do think there's a little bit more promising subgroup analysis from the isatuximab data in the context of renal dysfunction that may guide some folks in that direction as we gain more and more clinical experience with that as a drug.

Dr. Maples: Yeah, I would agree. I think it's definitely something that's going to continue to change. We can take a look at some of that data that we do now have available.

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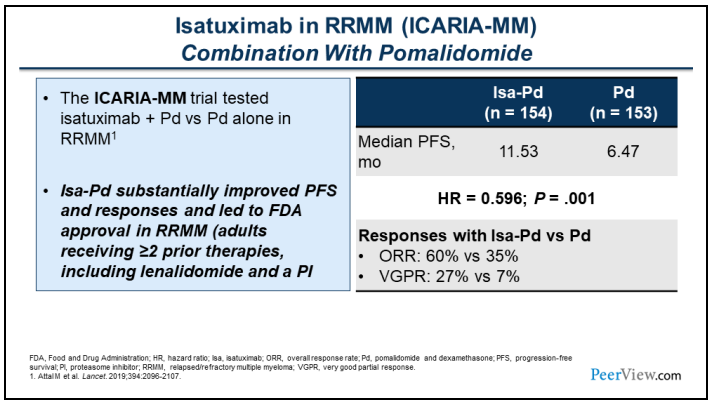

Isatuximab was approved in combination with pomalidomide and dexamethasone for patients with relapsed/refractory myeloma based on the ICARIA trial. This trial showed that the median progression-free survival was improved with the isatuximab arm to 11.5 months versus around 6.5 months with pomalidomide/dexamethasone alone. This led to the initial approval of isatuximab in those who have had 2 prior therapies, including lenalidomide and a proteasome inhibitor.

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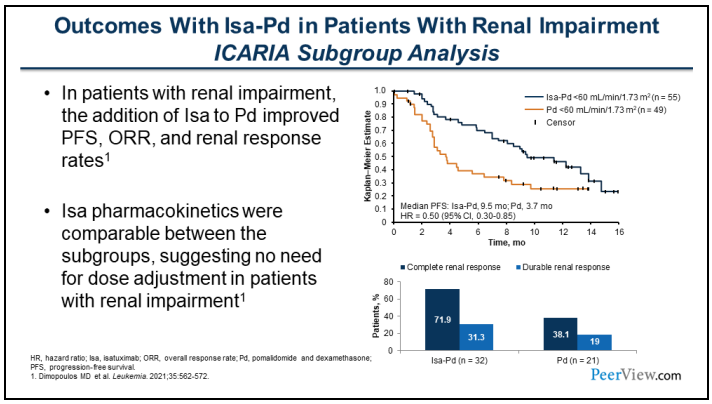

An additional subgroup analysis from this ICARIA trial in patients with renal impairment was conducted, and what this analysis showed was that in patients with renal impairment, the addition of isatuximab to pomalidomide and dexamethasone improved progression-free survival, overall response rate, as well as the renal response rate. We saw some improvement in renal dysfunction, which is always important because we want to try to save their renal function when we can.

Isatuximab pharmacokinetics were deemed comparable between the subgroups, suggesting that there was no need for any dose adjustments in those patients with renal impairment.

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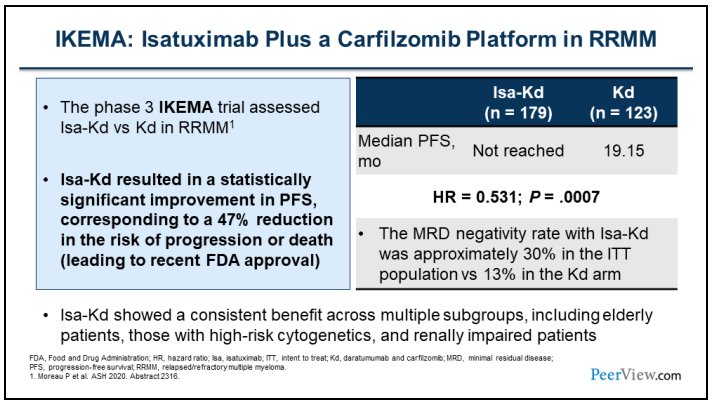

More recently, we saw the approval of isatuximab in combination with carfilzomib, and this came from the IKEMA trial, in which it was isatuximab/carfilzomib/dexamethasone versus carfilzomib/dexamethasone alone. The median progression-free survival in the isatuximab arm was not reached versus 19 months with carfilzomib/dexamethasone alone.

We saw an improvement in MRD negativity rates, and we also saw that the benefit with isatuximab was consistent across multiple subgroups, including elderly patients, those with high-risk cytogenetics, and renally impaired patients. I think this is an important note to make because we're always looking for those patients with high-risk cytogenetics, what the best treatment for them is, as well as what's the best treatment for renally impaired patients.

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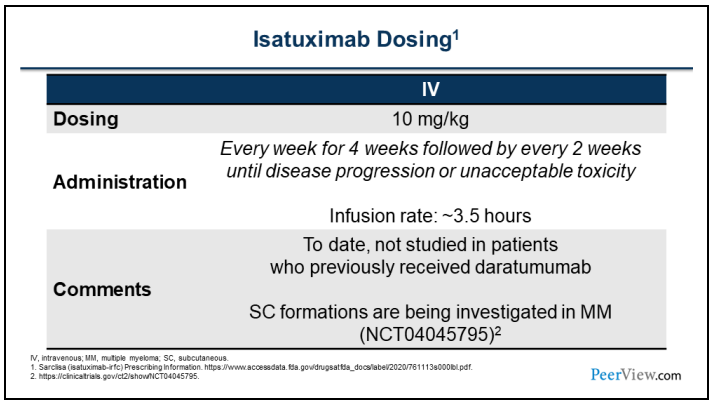

When looking at the isatuximab dosing—it's 10 mg/kg. It's a weight-based dosing given weekly for 4 weeks, followed by every 2 weeks thereafter. This is a little bit different than daratumumab in that we continue this agent every 2 weeks rather than going to monthly.

The infusion rate is shorter than that initial long IV daratumumab infusion. It's around 3.5 hours. Of note, today we don't have any data with this agent in patients who were previously treated with daratumumab. I think that is going to become important as we see daratumumab move to the frontline setting and how that may impact the role of all of the CD38 monoclonal antibodies in the relapsed space.

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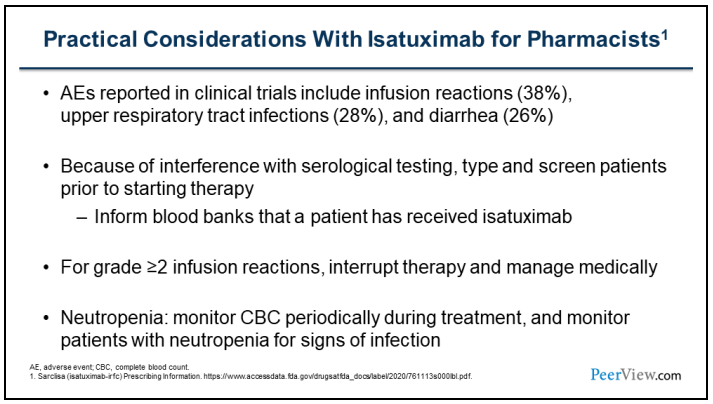

Here are some practical considerations to think about. We always want to be mindful of infusion reactions; as we discussed, most of them are grade 1 and grade 2, but premedicate and stop for any grade 2 or higher infusion reaction to medically manage and make sure that the patients are safe. We want to look out for any upper respiratory tract infections as well as diarrhea. Similar to daratumumab, isatuximab can interfere with serological testing, so get that type and screen done prior to starting.

We also see neutropenia with this agent in both the combination with pomalidomide as well as carfilzomib, so monitor CBCs periodically during treatment. We very commonly will use growth factor for these patients, so we can give them growth factor weekly while they're on this therapy if needed to support their neutropenia.

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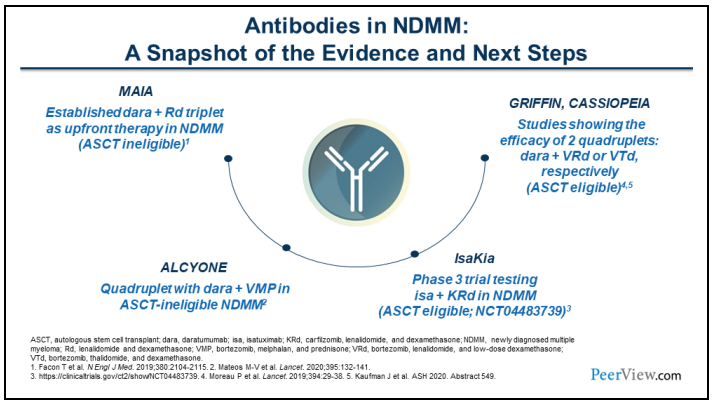

To summarize how we're seeing these antibodies move through the myeloma treatment landscape—we now are seeing daratumumab being utilized in the upfront setting in both transplant-ineligible and transplant-eligible patients.

We had our MAIA and ALCYONE data, in which we see daratumumab in the transplant-ineligible patient populations being used as frontline therapy and continued until progression, and then with GRIFFIN and CASSIOPEIA, we see the quad-based regimens with daratumumab being used in our transplant-eligible patients. We have isatuximab also being investigated in combination with carfilzomib, lenalidomide, and dexamethasone.

As we start to see these CD38s move to the frontline setting, it's going to impact how they're used in the relapsed space, and it may open up other options for some of our other treatments that we're going to be discussing as we continue through this discussion. I will turn it back over to Donald.

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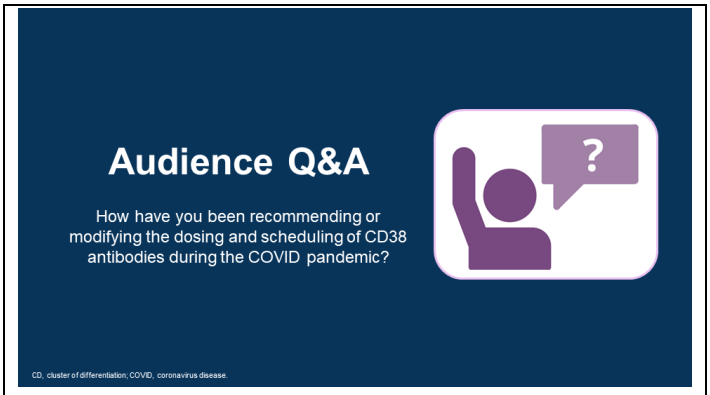


Dr. Harvey: Thanks, Kathryn. That was a fantastic review of the CD38 landscape, where we are, where we're going, and certainly creates a lot of opportunities for discussions.

We've got time for one question here. One thing I would ask you guys is—we are in the pandemic, and so—how have you been recommending or modifying any dosing or scheduling of CD38 antibodies during COVID? Are you doing anything differently at your practice sites based on the pandemic and patient desire or lack of desire to come to the center? Kathryn, I'll start with you.

Dr. Maples: Yeah, absolutely. We have not seen any change in our CD38 dosing per se. I think that is one benefit to daratumumab, going to that monthly dosing. The subcutaneous route has, of course, limited the amount of time that they're in the infusion center, so that's been great.

We have mostly modified the dexamethasone dosing. We've tried to dose-reduce or remove altogether in light of the pandemic. But Tim, we'd love to hear what you guys are doing.

Dr. Peterson: Basically along the same lines, we've really not changed the dosing schedule of daratumumab. With the timing of the pandemic and, as you mentioned, the NCCN guidelines immediately updating to incorporate the substitution for the subcutaneous formulation, we have pretty much made that entire interchangeability across the entire institution.

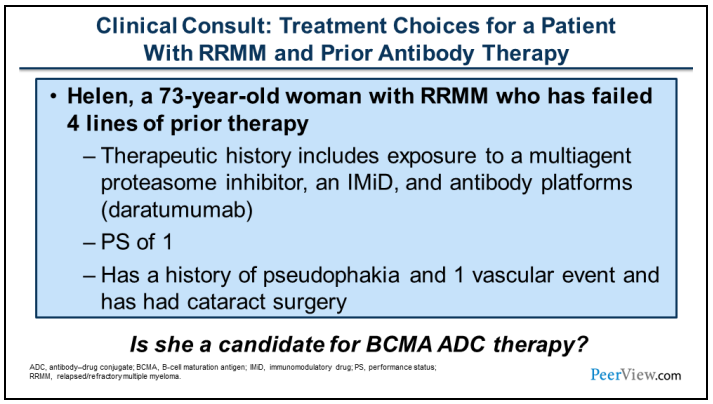
I will also point out that the isatuximab subcutaneous formulation is already being investigated because that's going to come through much quicker than the daratumumab subcutaneous formulation, so I think that will help going

forward, as well.

Dr. Harvey: Yeah, it's certainly a competitive landscape. We've got these antibodies. We've got other constructs with CD38 as part of them, so BiTEs in other areas, and it will be interesting to see how all this unfolds. Thank you both.

As we look now at where we can go, I'll take over and we'll talk through the first antibody–drug conjugate that has been brought forward in myeloma therapy in BCMA as a target.

Slide 23



We'll start off here again with a case. This is Helen, a 73-year-old woman with relapsed/refractory disease whose therapies have failed her on 4 occasions. I'm a big fan of saying that patients don't fail therapies, therapies fail them, although historically, we've gone the other direction.

Her history is such that she has had a multiagent proteasome inhibitor pathway of treatment, and IMiDs and antibody platforms as well. All these she's had in the past. She currently has good performance status at 1. She does have a history of pseudophakia and 1 vascular event and has had cataract surgery. Obviously, all those things come into play as we're considering an antibody–drug conjugate and specifically any therapy that will target BCMA.

I'll ask you guys. Tim and Kathryn, is this patient, in your mind, a candidate for BCMA antibody–drug conjugate therapy? Tim?

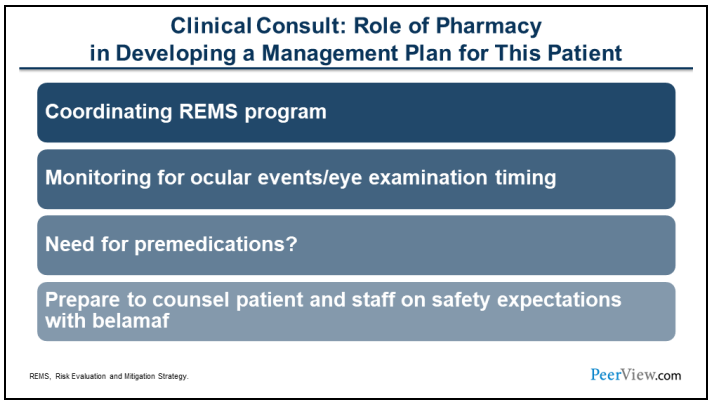
Dr. Peterson: I would say clearly, based on her prior lines of therapy, she satisfies the requirement for belamaf based on that context. She's of good performance status as well, so you would think she should be able to tolerate this therapy that's been shown to have very good response rates and durable responses.

Her ocular history there could bring up some flags for a little extra monitoring potentially, but I know you're going to speak to the REMS program and the very arduous process of ophthalmology clearance and very close monitoring, so I don't think that would be a red flag enough to cause any sort of severe precaution for this patient.

Dr. Harvey: All right. Kathryn?

Dr. Maples: Yeah, I would agree with that. I think Tim makes excellent points. I don't think her ocular history precludes her, and I think, considering our other options for this patient at this point, belamaf would be a great option for her.

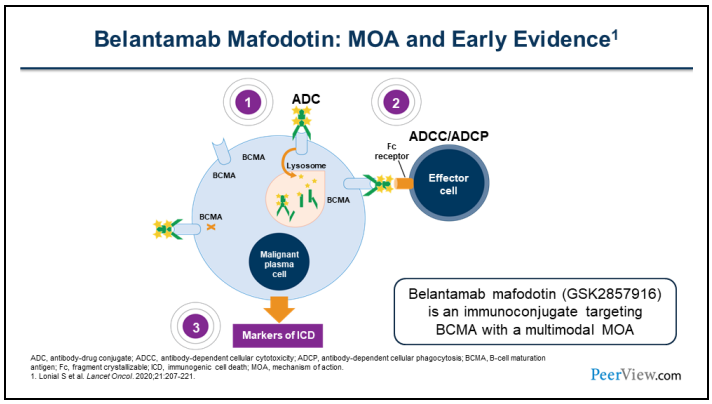
Slide 24



Dr. Harvey: All right. Well, let's get into that and think about what our role is in developing a management plan specifically for this patient. Tim, as you brought up, coordinating the REMS program is critical. There's a REMS program with belamaf that we'll talk through—what that means for ocular events, examinations of ocular function, and ophthalmologic examinations.

I'll ask you guys about your thoughts on premedications. We'll talk through that as well. It is an antibody–drug conjugate, and so premedications always come up with this. Certainly we need to prepare the patient for counseling, as well as staff and others who may not be as familiar with this agent and its use and how we might consider moving forward with the drug.

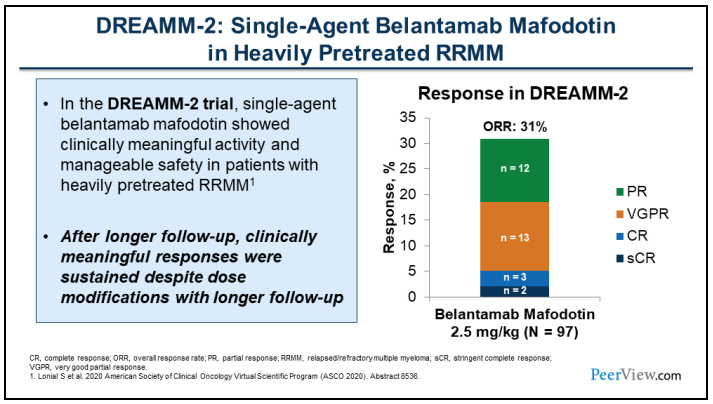
Slide 25



Let's talk about BCMA as a target and the first antibody–drug conjugate, the Trojan horse, for patients with myeloma. Any antibody–drug conjugate is going to link to an extracellular receptor and then deliver its payload internally and intracellularly.

That BCMA target is where this works. The payload, the mafodotin, the maytansinoid derivative, is then delivered and kills off the plasma cell as well. There are other mechanisms of how belamaf works, and it does appear to bring on some immune-related activities of ADCCs and other aspects of how additional therapy or additional mechanisms might be brought on to help belamaf continue to provide deep and sustained responses over time beyond its standard infusion and the period of time afterwards.

Slide 26



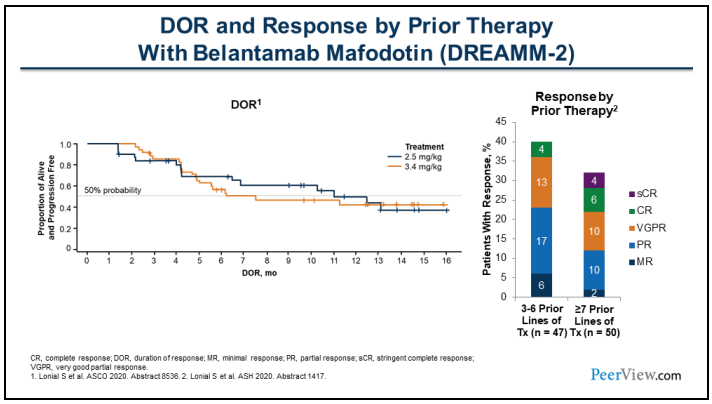
The data for belamaf come from DREAMM-2, which is a single-agent trial in patients who are pretty heavily pretreated when we look across the landscape. We are, to some degree, lucky to have the ability to continue in a heavily pretreated population with new drugs that have come forward in development and continue to be there.

In DREAMM-2, there was clinically meaningful activity and certainly manageable safety. Again, we'll go through the ocular events, but I think probably one of the most intriguing things to me about belamaf is that there are meaningful responses that occur that are longer in nature and longer in duration. It suggests that early therapy and where we go with therapy matters.

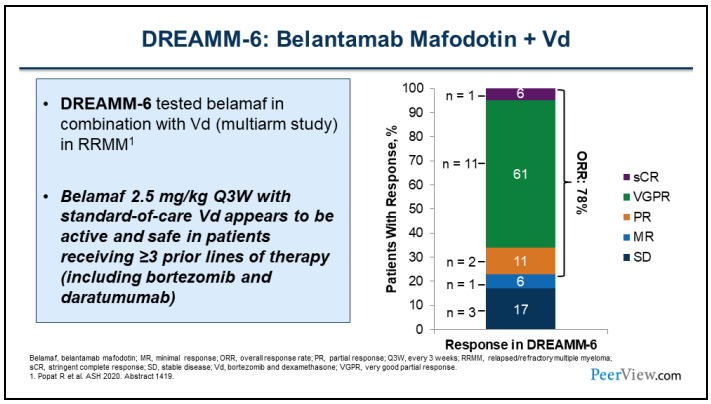
Afterward, perhaps there are some ideas around dose reductions and dose holds, and we can have a little bit of comfort if we need to do that because the responses that are induced early appear to be fairly prolonged when they do get achieved early on in treatment.

The overall response rate was 31% in DREAMM-2—again, a relatively low number. Note here the dose of 2.5 mg/kg, which we'll talk about, as well. But this was a 97-patient series.

Slide 27



Slide 28



This is some of the duration of response, and earlier in the development, the dose was escalated to 3.4 mg/kg, and I really applaud GlaxoSmithKline as well as the FDA for looking at all this data and saying, "You know what? Three-point-four mg/kg really is no better than 2.5 mg/kg." In many other aspects of oncology, we've gotten the dose wrong, in my opinion, in certain areas.

This was a time when there was pause and assessment of the dose and what it meant for patients' tolerability and response, and we showed that 2.5 was equivalent. That was the dose that moved forward for development and subsequent approval.

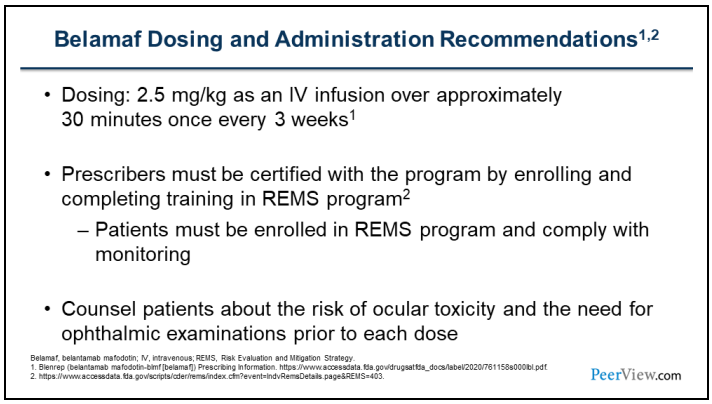
You can see (slide 27) some of the data on responses based on prior lines of therapy. Again, we have the ability in myeloma to treat with as many as 7 or more lines of treatment, and you can see within that group that there were really good response rates based on those prior lines of therapy in those 50 patients, with upwards of PR and VGPR, et cetera, being seen in a substantial proportion of individuals. So it is an active agent in those very heavily pretreated patients.

DREAMM-6 combined belamaf with bortezomib and dexamethasone. You can see (slide 28), again, this was a 2.5-mg/kg dosing strategy, every 3 weeks, with a standard-of-care combinatorial therapy with bortezomib and dexamethasone. Again, these were patients with 3 or more prior lines of therapy, which included bortezomib previously as well as daratumumab.

The 78% overall response rate, again, should give us hope and promise that patients with pretreated disease certainly are effectively treated with belamaf in many instances.

Even stringent CR is seen in, again, 1 patient out of the cohort, but it's still promising in terms of what was seen in this heavily pretreated combination treatment therapy.

Slide 29

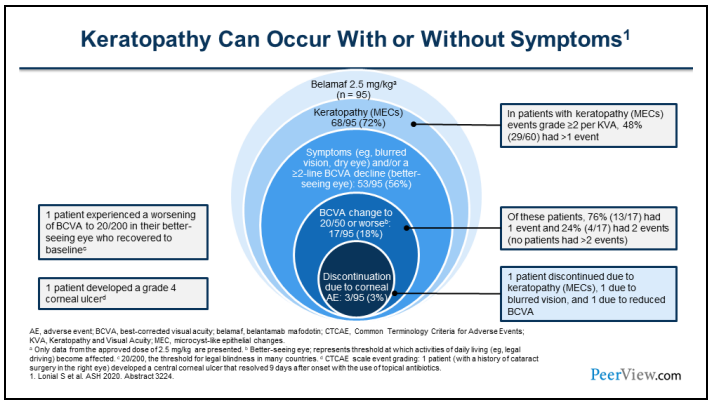


Overall belantamab dosing and administration are listed (slide 29). It's FDA approved at 2.5 mg/kg over 30 minutes given every 3 weeks. There is a REMS program, and prescribers must be certified with that program and be enrolled and complete training within it. Patients must also be enrolled.

This is a REMS program, but let's be candid. Myeloma is not new to REMS programs. We've been dealing with this for many years with the IMiDs and thinking about that, and certainly it's a different type of REMS, but it's still not something that's brand-new to the field.

Patients do need to be counseled about the risk of specifically ocular toxicity. BCMA is expressed in ocular tissue, and, similarly, mafodotin as a carrier can enter the ocular space. That's really the driver of some of the adverse events that we have to consider and be mindful of as patients begin therapy.

Slide 30



Keratopathy is the overall description of any ocular event seen with belamaf, and this is a nice depiction of what might be seen within that 95-patient cohort who receives 2.5 mg/kg over an every-3-week period.

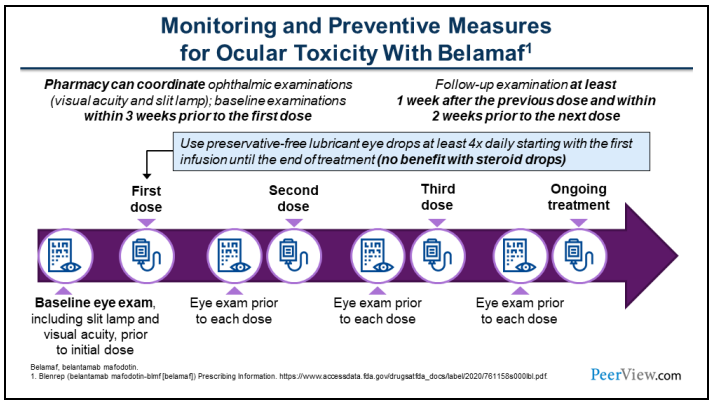
You can see keratopathy by exam—this is an ophthalmologic examination—and 72% of patients did have some event that was graded as 2 or higher, and 48% had more than 1 event. Again, that's by examination. Not all of these patients were symptomatic.

But if we move into the next circle, symptoms can occur in a little over half of patients, and there might be a slight visual decline in these patients that can be seen based on prospective evaluations as well as examinations by ophthalmology colleagues.

Of those patients, again, 17 of the 95 had a change in vision by Snellen testing or otherwise to 20/50 or worse. That needs to be considered, and patients having changes in vision need to be thought of very differently and carefully as we move forward.

Finally, probably an important point is that the drug had to be discontinued in 3 out of the 95 patients secondary to these events. So these can happen. They need to be monitored. These are rarely permanent and almost never permanent in terms of adverse events for the eyes. They are reversible with drug holding and dose reduction. Thinking about this as a prospective event is important in patients who can get it.

Slide 31



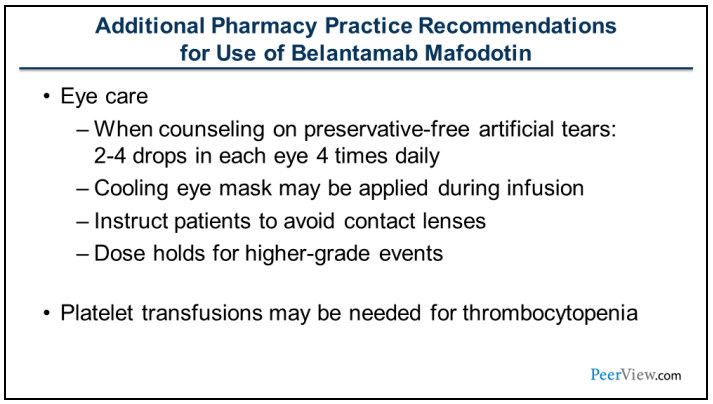
Think about monitoring and preventing it; certainly, baseline exams are critical, and this is where pharmacists can be incredibly important in coordinating these ophthalmologic exams. These are visual acuity and slit lamp. These are standard exams for patients that ophthalmologists and eye specialists do within 3 weeks prior to the first dose. It needs to be within that window.

Another critically important point for pharmacists to tell patients is that patients do need to use lubricant eye drops at least 4 times a day beginning with the first infusion until the end of treatment. Unlike in other areas of oncology that we rage about as pharmacists—high-dose cytarabine as an example of eye drops—really, there's no benefit with corticosteroids.

This was seen early on in the belamaf development, and we're lucky at Emory to have early experience with this agent. There was really no benefit to steroids, and so patients should really be provided lubricants. Again, it's a somewhat similar concept as cytarabine. You're looking to wash the drug out of the eye to maintain a moist area so that the likelihood of these adverse events can be minimized.

Exams have to be prior to each dose, and that exam and those results need to be communicated back to the patient's myeloma provider. Sometimes, it takes some chasing down, and that's where I think pharmacists can certainly be critical in helping the care team to obtain this information and to ensure follow-up for patient safety. Ongoing therapy is there, as well.

Slide 32



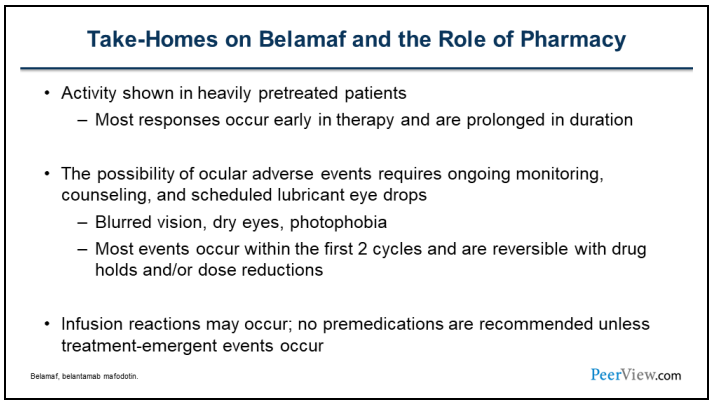
Some other pharmacy recommendations—again, eye care is critical. A cooling eye mask may be applied during the infusion to try to reduce vascular delivery of the drug to the ocular space. There are some ideas, although not proven yet, about vasoconstrictors that might be used prior to and during infusion therapy, as well. That's ongoing side-by-side evaluations, but there are no clear recommendations as of today.

Patients should avoid contact lenses to ensure that the drug itself is not maintained on the ocular surface as a cover by the contact lens.

Again, with higher-grade events, as measured by eye care specialists, the drug does need to be held. When we talk about responses, we can feel fairly confident that those drug holds really shouldn't impact disease response overall in most patients.

Then finally, it is an antibody–drug conjugate with a maytansinoid as a payload, and so platelet transfusions may be needed secondary to thrombocytopenia that can be seen with this drug.

Slide 33



Here are some take-home points on belamaf and the role of pharmacy (slide 33). Again, there is activity in heavily pretreated patients, so we need to maintain this as an option in those folks. Ocular adverse events do require ongoing monitoring, counseling, eye drops, and making sure patients understand to use them.

Patients' symptoms may include blurred vision, dry eyes, and photophobia, and so if a patient comes to you with those adverse events, an exam is important to make sure prior to the next dose that that's assessed.

Most events do occur, however, within the first 2 cycles. In about 40% of patients who have these events, it happens within the first couple of cycles, so vigilance early is important. You can have vigilance later on, but you should know that the frequency is likely to happen earlier.

Infusion reactions may occur overall. Within the product information, there's no premedication that's recommended, but treatment-emergent events may occur, and we might have to implement premedications for subsequent infusions should reactions take place.

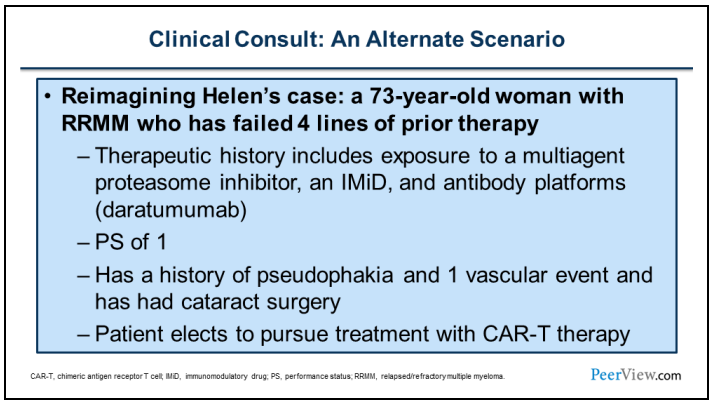
With that in mind, I think we can talk a little bit about belamaf and what we might do with premedications. I'd ask you, Tim and Kathryn, what kinds of things do you think about with premedications, and how should we consider them for treatment-emergent adverse events?

Dr. Maples: Yeah, I think the premedication around belamaf is a hot topic. We, at our institution, do premedicate all patients starting from cycle 1 with acetaminophen and diphenhydramine. Our experience in the DREAMM trials, we saw a lot of patients having reactions, so we went ahead and just built that into our standard order set, so all patients get premedicated. Tim, what are you guys doing?

Dr. Peterson: That's very interesting. I think you'd probably get a different answer at most institutions you talk to about this. We thought the opposite. We went with the low rates of infusion-related reactions that happened, so we do not routinely premedicate patients with their first dose, but if they have any sort of mild reaction, we will premedicate them going forward. It'll be interesting to see what practice is like at other institutions, knowing that just between the two of ours, it's vastly different.

Dr. Harvey: Interesting. All right. With that, we'll move into perspectives on the emergence of BCMA-directed CAR-T cell. Tim?

Slide 34



Dr. Peterson: Okay, great. Thank you. We're going to switch gears now to discuss BCMA-directed CAR-T cell therapy in relapsed and refractory multiple myeloma, but before we do that, I want to revisit our patient case. We're looking at the same woman who had received 4 prior lines of therapy. Again, this included a proteasome inhibitor, an immunomodulatory agent, as well as a CD38-targeted monoclonal antibody.

Notably to me now, she is of good performance status, which we discussed, ECOG performance status of 1. She elects to pursue treatment with CAR-T cell therapy, which I'm sure you've seen at your institution. Commercial CAR-T cell has been a hot topic in multiple myeloma, and we've been looking forward to this for years now.

I'd like to open it up and get your thoughts regarding this patient, who now does qualify for both of our commercially available BCMA-directed therapies—belamaf and our newly FDA-approved idecabtagene vicleucel. Dr. Harvey, if you want to start, what sort of considerations do you think would go into deciding belantamab versus CAR-T cell therapy for this patient?

Dr. Harvey: That's a good point. I mean, when you look at someone who's this heavily pretreated with a PS of 1, to me, that's always the first question. Then you have to think about some of the social issues in terms of support and what do they have? It's not quite an allogeneic transplant, but we do need to make sure that, particularly with CAR-T cell therapy, there is a good support network that's there.

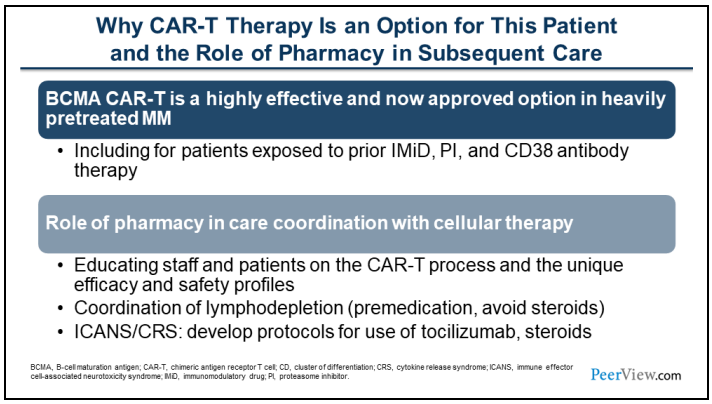
Think about options for durability and what are the implications of sequencing one then the other versus the other direction? Do we have experience with patients getting one BCMA-directed therapy and then doing well or not well on a subsequent BCMA-directed therapy, which is, I think, all part of the mix. Those are the things that I would start to think about in this individual case. Kathryn, how about you?

Dr. Maples: Yeah, I completely agree. I think the sequencing thing is the biggest question for me. If you punch your BCMA ticket, is it a one-time thing or can you use something else?

I think for her, considering her age and her performance status, if she personally chooses to go the CAR-T route, I think she would be a good candidate for that as long as she has the support system. It's a good option for someone who doesn't want to have to go on ongoing therapy. The CAR-T cell route would not need ongoing maintenance afterward, and that might be desirable for her at her age.

Dr. Peterson: Great. Those are all great considerations, and clearly, there are a lot of different variables that go into the selection of agents and sequencing with regard to CD38-targeted antibodies. Now with BCMA becoming part of the clinical picture, it's going to be an ever-present question going forward.

Slide 35

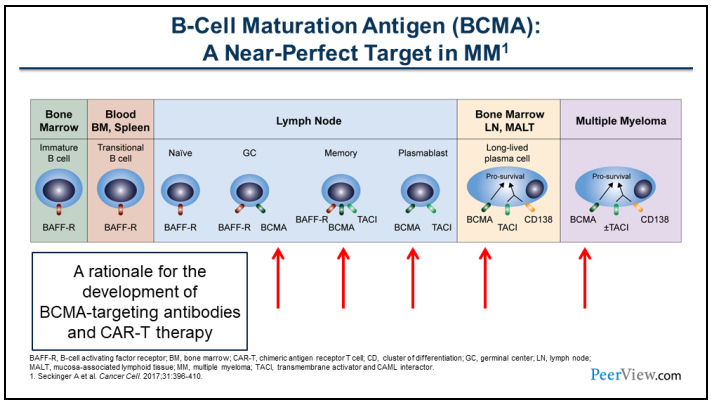


Looking at CAR-T cell therapy in multiple myeloma, there are a lot of unique roles that pharmacists can play. We have unique opportunities to provide education to both staff and patients regarding the CAR-T cell process, including the unique efficacy endpoints and safety profiles associated with the CAR-T cell constructs.

There's also the education process and coordination of lymphodepletion, and lymphodepletion for these CAR-T cell constructs consists of conventional chemotherapy. We're talking about sequelae associated with those as well, in preventing adverse events, nausea, hemorrhagic cystitis, and those sorts of things that can be seen with those agents.

Importantly, since we just had FDA approval of our first commercial CAR-T cell in multiple myeloma, we're going to see a lot of providers and clinical staff that are not necessarily used to CAR-T cell provision and utilization, so it's an important opportunity for clinical pharmacists and pharmacy administration to be actively involved in the development and implementation of the guidelines and standard of practice for the management of cytokine release syndrome and neurotoxicity that we've seen with prior CD19-targeted CAR-T cells.

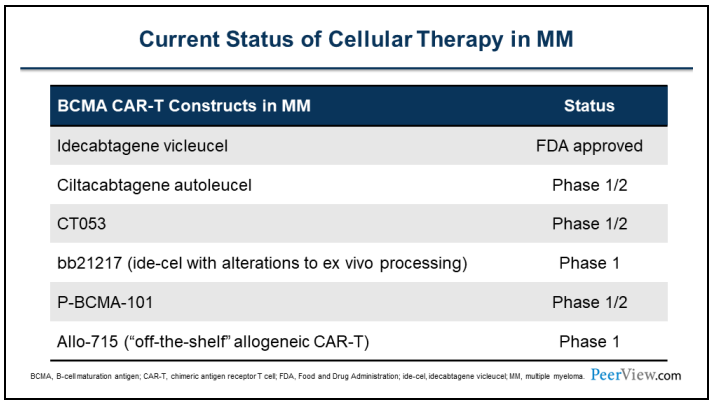
Slide 36



Dr. Harvey already mentioned why BCMA is a very good target for plasma cell disorders, but looking at this image here (slide 36), we can see that expression of BCMA is enhanced during the B-cell differentiation process.

The further to the right, basically, we can see higher expression of BCMA, particularly in those late-memory B cells and plasma cells, making it very much so an ideal therapeutic target for multiple myeloma and other plasma cell disorders.

Slide 37



Current Status of Cellular Therapy in MM

BCMA CAR-T Constructs in MM	Status
Idecabtagene vicleucel	FDA approved
Ciltacabtagene autoleucel	Phase 1/2
CT053	Phase 1/2
bb21217 (ide-cel with alterations to ex vivo processing)	Phase 1
P-BCMA-101	Phase 1/2
Allo-715 ("off-the-shelf" allogeneic CAR-T)	Phase 1

BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; FDA, Food and Drug Administration; ide-cel, idecabtagene vicleucel; MM, multiple myeloma. PeerView.com

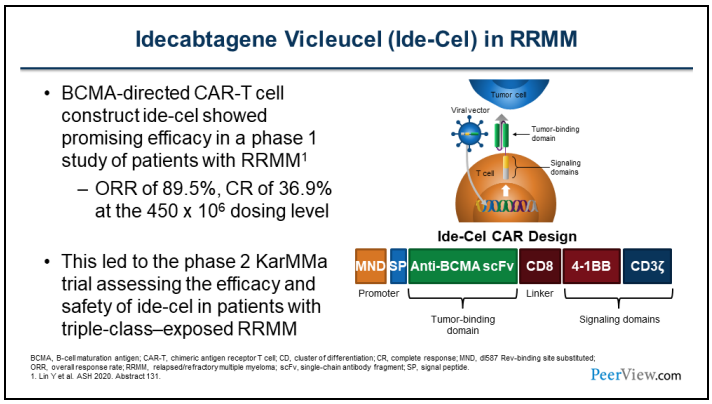
Thinking about the current landscape in CAR-T cell therapy, specifically targeting BCMA, we have the first agent here, which is idecabtagene vicleucel, or ide-cel, and this was just very recently FDA approved. We also have ciltacabtagene autoleucel, or cilta-cel. The manufacturer for this one has submitted for rolling submission of its biologic license application, so it's also very far along in investigation.

We have additional BCMA-targeted autologous CAR-T cells as well. CT053, some preliminary results were published at ASH this past year (2020) looking at the LUMMICAR-2 study. We have bb21217, which may sound familiar because ide-cel was formerly known as bb2121. This is the ide-cel CAR-T cell construct with some alterations made to the ex vivo processing, specifically incorporation and introduction of a PI3K inhibitor. The idea is that this can help to potentially increase the proliferation and persistence of the CAR-T cell construct in vivo.

The last autologous BCMA CAR-T cell construct that's listed here (slide 37)—again, not an exhaustive list—is P-BCMA-101. Similarly, had some updated results, very preliminary results that were presented at ASH this past year, as well.
In addition to that, we're also starting to see investigation of off-the-shelf CAR-T cells, which are allogeneic CAR-T cells. There are a few obvious benefits to this. One would be reduction in the manufacturing time, and not necessarily requiring bridging therapy after leukapheresis for an autologous CAR-T cell patient.

There's also the theoretical thought that if we're using healthy donors and healthy volunteers, we're likely to have more competent T cells that are harvested for utilization, and we may see a more profound effect compared with T cells that are harvested from a multiple myeloma patient or a lymphoma patient who's undergone myelosuppressive and immune-suppressive therapies.

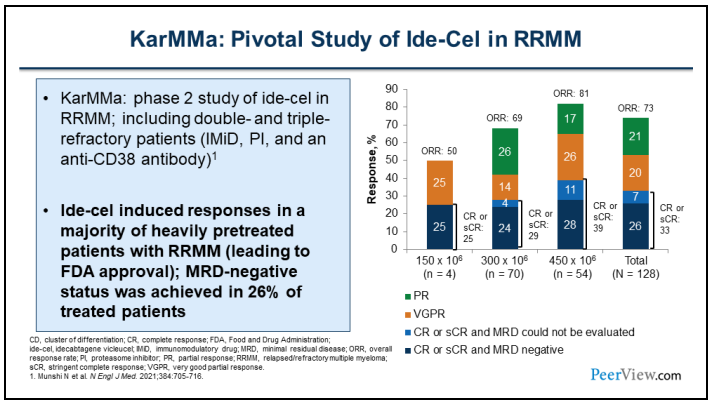
Slide 38



Looking at idecabtagene vicleucel, it initially showed its initial efficacy and safety in a phase 1 study. Some of the updated results were presented at ASH this past year (2020). You can see, obviously, very high response rates, near 90%, with nearly 40% at the highest dosing level attaining a complete response.

Looking at the construct itself (slide 38), the tumor-binding domain clearly is targeting BCMA, the linker to our signaling domains. It does utilize the very commonly used costimulatory domain of 4-1BB. Based on the manageable toxicity profile that was shown in this phase 1 study and the very high and deep response rates, it's what led to the phase 2 KarMMa study.

Slide 39

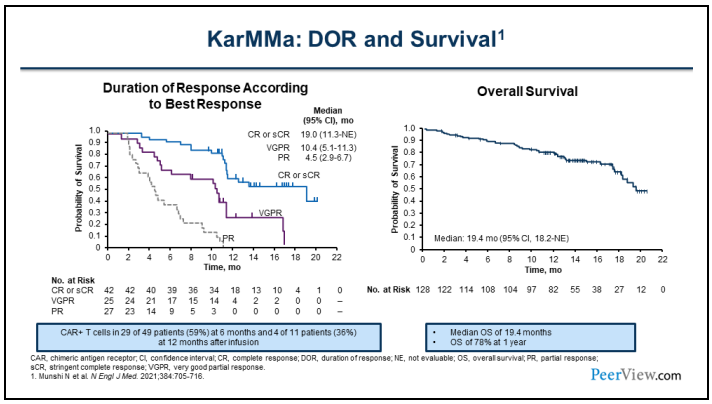


This is our pivotal phase 2 study of ide-cel that ultimately led to its FDA approval. In this study, they enrolled patients who had received at least 3 prior lines of therapy, and that had to have included an immunomodulatory agent, proteasome inhibitor, and a CD38-targeted monoclonal antibody.

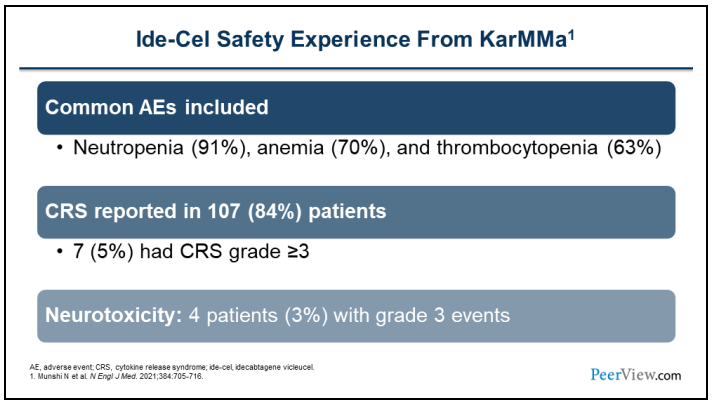
Ultimately, the patients who were enrolled had received a median of 6 prior lines of therapy, and 84% of those patients were deemed to be triple-refractory when they came in. This is a very heavily pretreated patient population that can clearly be very difficult to treat with safe and effective options.

If you look on the right (slide 39), you can see the response rates based on dosing utilized. If we look at all comers, the overall response rate was very high, 73%, with 33% of patients attaining a CR or a stringent CR. But then if we look at dosing level, if you look from left to right, you'll see that there were higher response rates, as well as deeper responses that were experienced in patients who received the 300 x 10^6 and 450 x 10^6 dosing groups.

Slide 40



Slide 41



The median duration of response for all comers was 10.7 months, but the response was increased with increasing depth of their response, so the duration of response was actually 19 months for patients who attained a CR or stringent CR. Clearly, with deeper responses, we're seeing more durable responses as well, which was what would be expected. The median overall survival was over 19 months, and at 1 year, the overall survival was 78%.

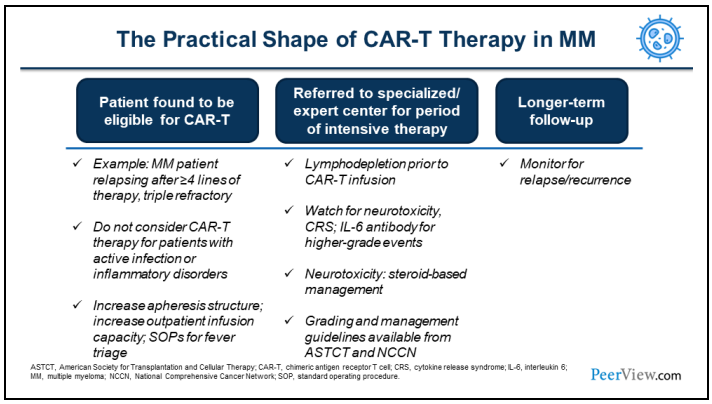
When looking at CAR-T cell constructs, it's also important to think about the persistence and proliferation of the CAR-T cell construct. What they did is they looked at 6 and 12 months, and respectively, they found that CAR-T cell construct to still be persistent in 59% and 36% of patients who were investigated for the persistence of the CAR-T cell.

The toxicity profile for ide-cel is largely what's been expected and experienced with CD19 CAR-T cell therapies. This does include rare but very severe potential adverse effects. The most common adverse events included hematologic toxicities, most predominantly neutropenia. Infections were noticed in 69% of patients; 22% of those had grade 3 to 4 toxicities.

If we look at all patients at all dosing levels, 84% of patients experienced cytokine release syndrome, which we know to be associated with CAR-T cell therapy. Most of these were mild grade 1 to 2 toxicities, with only 5% of patients having CRS of grade 3 to 4.

Similarly, we know neurotoxicity to be associated with CAR-T cell therapy, but only 18% of patients in all dosing cohorts experienced all-grade neurotoxicity, and only 3% of those patients experienced grade 3 neurotoxicity, with no grade 4 neurotoxicity reported. It's important to note that cytokine release syndrome and neurotoxicity occurred with greater frequency in the higher-dosing cohorts, as you might expect.

Slide 42



When we think about practical considerations for CAR-T cell therapy in multiple myeloma, first we need to obviously identify the appropriate patients. The current indication for our only FDA-approved CAR-T cell therapy is after at least 4 prior lines of therapy in patients who have been exposed to a proteasome inhibitor, immunomodulatory agent, and a CD38 monoclonal antibody.

Similar to our CD19 CAR-T cells, we shouldn't be using these in patients who have active infection or inflammatory disorders, and around the lymphodepletion period, you may delay CAR-T cell administration up to 7 days for serious adverse events that are unresolved.

We need to also increase the bandwidth—both inpatient and outpatient—for these myeloma services to increase our access to infusion centers and develop guidelines and standard of practice for triage of patients who have symptoms suggestive of cytokine release syndrome or neurotoxicity.

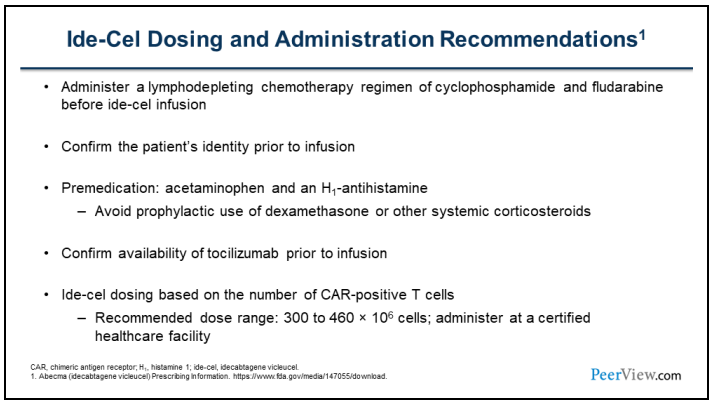
Thinking logistically through, we have our lymphodepletion process, which consists of cyclophosphamide and fludarabine administered intravenously on a daily basis for 3 days, and then ide-cel is subsequently administered 2 days later.

We're monitoring these patients acutely for neurotoxicity and cytokine release syndrome, knowing that for the latter we have our IL-6 receptor antagonist tocilizumab available. For neurotoxicity, we know that the IL-6 receptor antagonist is ineffective, so we're looking more at supportive care and steroid-based management.

There are some great management guidelines that have been published by the National Clinical Practice Guidelines that hope to allude to some of the more nuanced suggestions regarding management of these toxicities, as well.

Thinking longer-term, clearly we've seen that these can have very durable responses, so we're looking for relapse and recurrence. We do know multiple myeloma is still an incurable malignancy, but as we get more experienced with these different CAR-T cell constructs, the different costimulatory domains and targets that we're utilizing, we're going to be looking more and more at the persistence of the CAR-T cell construct and the proliferation of those T cells.

Slide 43



Here are some administration considerations (slide 43). We do have the lymphodepletion that we mentioned of cyclophosphamide and fludarabine prior to ide-cel. The second bullet is referring to the fact that this is still an autologous CAR-T cell therapy. We mentioned that we are investigating allogeneic CAR-T cells, but these are patient specific. Premedication for ide-cel is actually just acetaminophen and an H_1 antagonist given on day 0.

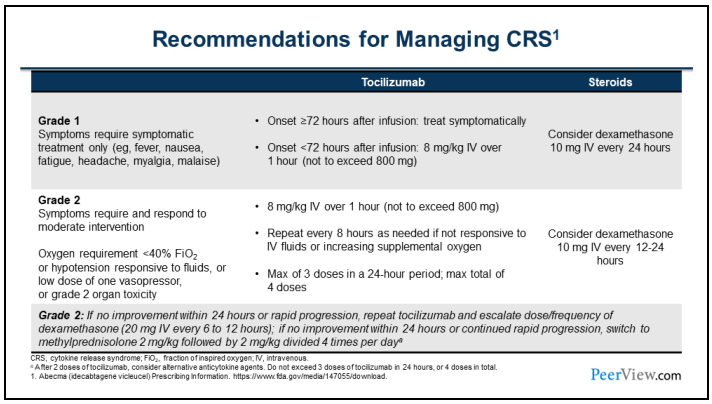
We do want to try to avoid prophylactic use of steroids. This is important to keep in mind when thinking about the lymphodepletion that we're using. The dose of cyclophosphamide that's used for lymphodepletion is 300 mg/m^2, which would typically be classified as moderate immunogenicity. Typically, we'd be thinking about steroids for the antiemetic regimen here, but that was omitted in the clinical trials, and it's largely still omitted in clinical practice. The idea is that steroids could potentially inhibit the proliferation of T cells.

Now, a caveat to that is that in recent years, we've seen multiple experiences published that are suggesting that our initial thought process regarding how extensive steroids may be able to inhibit the proliferation of T cells might have been a little overdrawn, and it may not be as extensive as we thought.

However, the KarMMa study, which led to the FDA approval of ide-cel, did not allow steroid doses above physiologic doses within 72 hours of lymphodepletion, and in clinical practice, we do still limit exposure to steroids around this time.

In accordance with the REMS program that's associated with ide-cel's approval, we need to make sure, similar to the CD19 CAR-T cell therapies, that we have 2 doses of tocilizumab that are available for every single CAR-T cell patient prior to infusion. You can see on the bottom (slide 43) the dosing range that's recommended based on the KarMMa study.

Slide 44



Recommendations for Managing CRS[1]

	Tocilizumab	Steroids
Grade 1 Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)	• Onset ≥72 hours after infusion: treat symptomatically • Onset <72 hours after infusion: 8 mg/kg IV over 1 hour (not to exceed 800 mg)	Consider dexamethasone 10 mg IV every 24 hours
Grade 2 Symptoms require and respond to moderate intervention Oxygen requirement <40% FiO_2 or hypotension responsive to fluids, or low dose of one vasopressor, or grade 2 organ toxicity	• 8 mg/kg IV over 1 hour (not to exceed 800 mg) • Repeat every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen • Max of 3 doses in a 24-hour period; max total of 4 doses	Consider dexamethasone 10 mg IV every 12-24 hours

Grade 2: *If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose/frequency of dexamethasone (20 mg IV every 6 to 12 hours); if no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day[a]*

CRS, cytokine release syndrome; FiO_2, fraction of inspired oxygen; IV, intravenous.
[a] After 2 doses of tocilizumab, consider alternative anticytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.
1. Abecma (idecabtagene vicleucel) Prescribing Information. https://www.fda.gov/media/147055/download.

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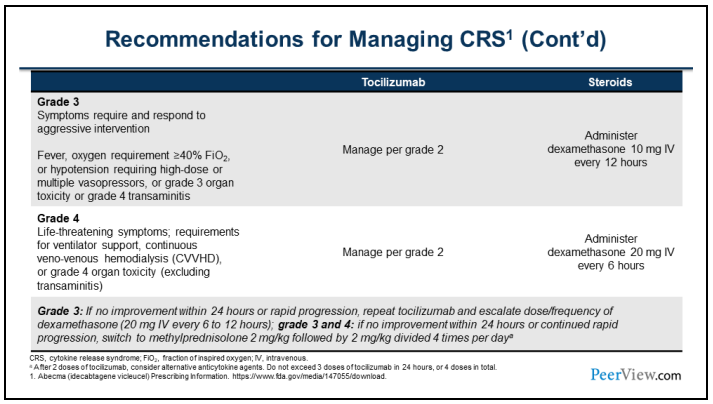
Slide 45



Recommendations for Managing CRS[1] (Cont'd)

	Tocilizumab	Steroids
Grade 3 Symptoms require and respond to aggressive intervention Fever, oxygen requirement ≥40% FiO_2, or hypotension requiring high-dose or multiple vasopressors, or grade 3 organ toxicity or grade 4 transaminitis	Manage per grade 2	Administer dexamethasone 10 mg IV every 12 hours
Grade 4 Life-threatening symptoms; requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD), or grade 4 organ toxicity (excluding transaminitis)	Manage per grade 2	Administer dexamethasone 20 mg IV every 6 hours

Grade 3: *If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose/frequency of dexamethasone (20 mg IV every 6 to 12 hours);* ***grade 3 and 4:*** *if no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day[a]*

CRS, cytokine release syndrome; FiO_2, fraction of inspired oxygen; IV, intravenous.
[a] After 2 doses of tocilizumab, consider alternative anticytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.
1. Abecma (idecabtagene vicleucel) Prescribing Information. https://www.fda.gov/media/147055/download.

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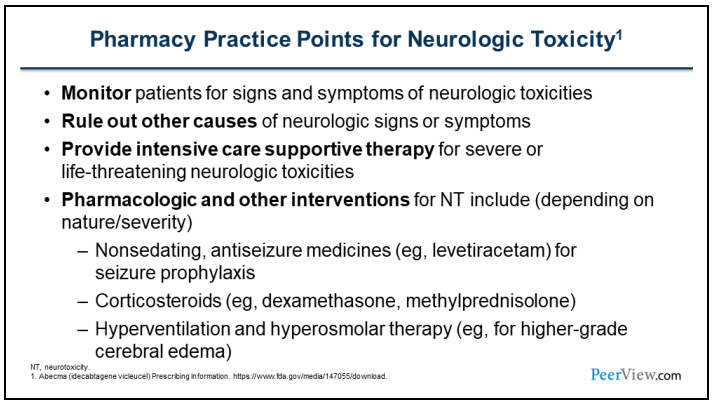
It's also important to keep in mind what the actual signs and symptoms are for cytokine release syndrome, the most common being fever, hypotension, and respiratory compromise.

When we look at early-grade or low-grade cytokine release syndrome, even if it's low grade but early-onset, it's still recommended to use our IL-6 receptor antagonist tocilizumab. Standard dosing would be 8 mg/kg. This can be repeated up to every 8 hours, for a max of 3 doses in 24 hours, and a maximum of 4 total doses through the course.

We're also looking at administering low doses of dexamethasone. As you see (slide 45), increasing grading of cytokine release syndrome, we're going to continue utilizing tocilizumab at the same dosing schedule, but we're seeing escalating doses of steroids and dose frequency of those steroids. That's in accordance with the severity of the symptoms, which, at this point, we're looking more at hypotension potentially requiring vasopressors, as well as respiratory compromise and higher oxygen demand.

Slide 46

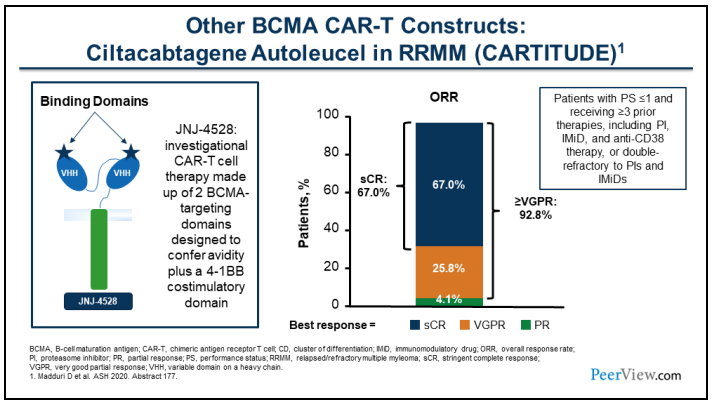


For neurotoxicity, we're monitoring patients for confusion, encephalopathy, tremors, and seizure-like activity. We do still need to rule out other causes. A lot of times we will need to get head imaging for these patients just to make sure there's not anything else that coincidentally happened in this time period.

For pharmacologic interventions, I mentioned that IL-6 receptor agonists are not used in this context, so we're looking more so at corticosteroids, primarily dexamethasone. Regardless of the grade of neurotoxicity, it's actually recommended to start nonsedating antiseizure medications prophylactically, and more often than not, this is going to be levetiracetam.

For the last portion here, for very high-grade cerebral edema, very serious toxicity, we can utilize hyperventilation and hyperosmolar therapy, but this would be very rare.

Slide 47

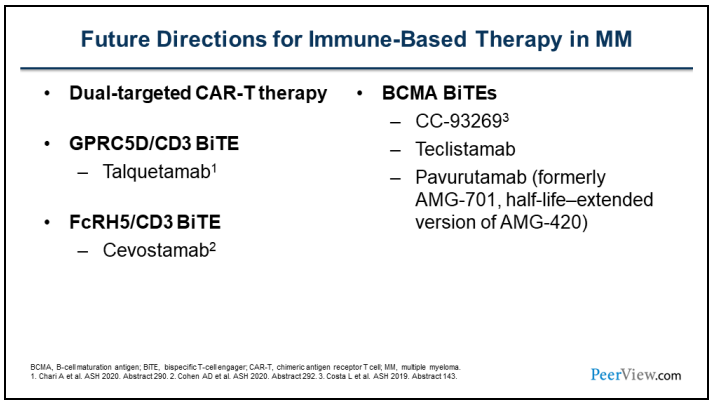


This is our honorable mention for BCMA-targeted autologous CAR-T cell, ciltacabtagene autoleucel (slide 47). I already mentioned this is under the rolling submission of its biologic license application. This actually has two BCMA-targeted domains—the idea here is to confer additional avidity. It has the same costimulatory domain as ide-cel.

Efficacy and safety were initially shown in the LEGEND-2 study that was completed in China. For the ongoing CARTITUDE study, some of the preliminary results were presented and are displayed here. Of note, this is a very heavily treated patient population as well, with a median of 6 prior lines of therapy. But we saw very high response rates and actually very deep responses.

Not all patients were assessed for minimal residual disease, but of the 52 patients who were, more than 90% of them were able to attain MRD negativity. This is an additional exciting BCMA-targeted autologous CAR-T cell construct.

Slide 48



Looking at future directions for immune-based therapy, we're looking at additional targets beyond BCMA. Obviously, we have numerous BCMA-targeted therapies that are being studied. GPRC5D and FcRH5 are both showing very promising results in the bispecific T-cell–engaging area, as well as dual-targeted CAR-T cell targeting those two in addition to BCMA for potentially increased binding affinity and efficacy that's been shown in early data.

We also have multiple BCMA bispecific T-cell engagers that are being studied. Clearly not an exhaustive list here (slide 48), but I will point out that AMG-420 is showing very good results. Its half-life was on the order of the half-life for blinatumomab, which we may know, because of that half-life, it needs to be given as an IV continuous infusion.

They actually developed a half-life–extended version, which is AMG-701, which is currently being studied and has similar efficacy, but does not need to be given in that continuous infusion, which is helpful obviously for both patient quality of life and institutional policies and procedures. I think with that, actually, I'll send it back to Dr. Harvey.

Dr. Harvey: Thanks, Tim. You know, the world of CAR-T cells continues to expand, and it's pretty exciting stuff coming forward in terms of what we might have in the future.

Slide 49

We've got time for one question, and it looks like one's come in about the general role of pharmacists beyond what we've talked about already with coordinating care with belamaf. I'll let you guys decide who wants to start off with that.

Dr. Maples: Yeah, I'll go ahead and jump in. I think that the pharmacist has several different roles that it can play with the REMS program with belamaf. From a clinic standpoint, the clinical pharmacist can be heavily involved in education of the patient from the get-go.

Help them get enrolled in the REMS program because signing that REMS enrollment is saying that they've been educated on the eye drops, on not wearing contacts, on things like that. It can seamlessly tie in with the education.

I know at my institution, I'm involved with helping touch base with the eye doctors, as well. Make sure that they have the forms and they know how to fill out the forms. If they have any questions, GlaxoSmithKline has great education programs that can help connect them with those people.

Lastly, the infusion pharmacist can play a big role as well because the final portion of the REMS is submitting what's called the REMS checklist—so signing off on the final milligram dose of the drug. Our institution has delegated that to the infusion pharmacist, so our infusion pharmacy manager is the authorized delegate for the infusion center, and then those pharmacists are the ones who go in and complete that. So I think the pharmacist can play roles all across the board, but Tim, I would love to hear what you guys do.

Dr. Peterson: Thank you. Yeah, it's definitely very interesting to see the minor nuanced differences between

institutions and how we've decided to manage this.

At Memorial Sloan Kettering Cancer Center, it's one coworker and I who are the two clinical pharmacists in multiple myeloma. We function in much the same way as you, providing the education. We assist the clinical staff in registration in the REMS program and education of the staff and the patients regarding the REMS program.

I will also reiterate that, especially here in New York City, we have a lot of local ophthalmologists that we have to utilize because patients come from a large area. There are a lot of ophthalmologists who aren't familiar with this.

But GSK, as you mentioned, does have a very good education process for ophthalmologists, so it's been very easy to coordinate that and to provide education to ophthalmologists, so they're comfortable with providing these sorts of clearances.

I and our clinical pharmacist in multiple myeloma serve as the authorized representatives who basically look at the ophthalmology data with the oncologists since we're with them in the clinic and identify any need for dose holds or dose delays. Then we submit authorization that ophthalmology clearance happened and clear the patient to be infused before the chemotherapy pharmacy will actually admix the drug.

Similarly, we're the two who are responsible for completing the postdose checklist. We have a couple of rate-limiting steps that pharmacy is integral for to make sure that nobody slips through the cracks, but I think there are numerous areas within the REMS program that pharmacy has opportunities to take hold of.

Dr. Harvey: Great. That's really fantastic. I want to thank you both for really great presentations and discussions around where we are with antibodies, cellular therapy, and other immune-based treatments to come, hopefully, for patients with relapsed and refractory disease and newly diagnosed and throughout the spectrum.