IMMUNOTHERAPY FOR HIGH RISK NEUROBLASTOMA

DR. MODY: Thank you, Wendy, for that nice introduction. And next I want to introduce my team. On the furthest is Erika Mora, who likes to be called -- Dr. Erika Mora, our clinical pharmacist. And she is actually in today's talk going to talk about dinutuximab administration and the side effect profile. Next we have Elizabeth Hollenkamp, and she’s our clinical nurse specialist. She’s a part of the pediatric pain team and she helps us with our management of our patients with dinutuximab-induced pain. And next we have Rhonda McDougall, our pediatric nurse practitioner and our solid tumor nurse practitioner in our oncology program, and she takes care of all our neuroblastoma patients.

So thanks everybody, for coming. And first of all, I wanted to thank the organizers for inviting us and giving us the opportunity to present our work. I think this is obviously a relatively in topic, a topic in vogue. Like a lot of things in immunotherapy it has been talked about in various tumor models, whether it’s neuroblastoma, whether it’s ALL, or whether it’s melanoma, we thought this would be an opportune time, with dinutuximab getting FDA approval and a lot of the other centers are starting to use that for neuroblastoma and other indications. What we wanted to do is to truly present an interprofessional approach, where when you treat these patients. As exciting the therapy and effective the therapy is, it’s certainly not easy.

I just wanted to ask how many in the audience are taking care of neuroblastoma patients. So, very few hands. Thanks for coming for my pediatric colleague. We knew this is primarily an adult audience, but I think again, like
Wendy said, this is actually troubling for other indications. So ultimately, this and other immunotherapy is going to be part of your clinical practice, and hopefully, we will all learn something today. So I’m just going to move to the next slide. Again, I think Wendy did a tremendous job, so we can move in. In terms of disclosure, I am a scientific advisor for United Therapeutics, which actually makes dinutuximab, and I am study chair for Children’s Oncology Group ANBL1221, which is actually a study that also uses dinutuximab. There are no other faculty disclosures.

So in terms of learning objectives, especially knowing that now we have predominantly an adult audience, we’re going to define what is high-risk neuroblastoma and what is the role of immunotherapy in its management, and then we’re going to review the mechanism of action of dinutuximab. That’s going to be the first part of the slide, first part of our talk, and then I think Erika is going to take all of us through the side effect profile and administration of dinutuximab. Then we have some very nice patient vignettes and a mother’s story, and I think we’re going to talk about a three-patient vignette and a mother’s audio recording. Rhonda is going to do the patient vignette. And finally, we are going to talk about some multidisciplinary approaches and process improvements, and how we actually ultimately arrive to where we are able to deliver this therapy very safely. And Beth is going to talk about those things.

So just a primary neuroblastoma. Compared to any adult cancer, even the most common pediatric cancer, ALL is considered rare. ALL pediatric cancers, by NCI definition, are rare and orphan diseases. And neuroblastoma is the third
most common, with about 10.2 per million in kids who are less than 15 years of age. Exclusively neuroblastoma is a young kids’ disease. We occasionally, very, very rarely see an adult with neuroblastoma, but otherwise this accounts for all neuroblastoma patients that we see in North America. Neuroblastoma accounts for about eight percent of all childhood cancer. I said it’s a young kids’ disease, close to two years of age at diagnosis and 95 percent or more will be diagnosed before the age 10. Male-to-female ratio, very slight male preponderance. About two percent of the cases are familial in nature associated with ALK gene mutation, and they usually get diagnosed early before the year.

This is a busy slide. Do not read the slide. What it talks about is two staging systems for neuroblastoma. And compared to any of the TNM and other staging systems that are more familiar, this is a different staging system. And what I think the one on the left actually shows is the current International Neuroblastoma Staging System, which actually post-operative systems. So if you have a patient come in with a large mass and the surgeon does a fabulous job and resects that, you can actually downgrade that patient compared to the newer system, which we have moved to International Neuroblastoma Research Group classification. It’s actually image based like most of the tumors that you are familiar with.

It’s like when a patient comes in that has a CT, MRI, MIBG, you look at that stage and patient gets staged. The staging there is pretty straightforward: localized tumor, regional spread, metastatic disease. And neuroblastoma has a special staging called MS or 4S here for current classification where you have
young infants less than 18 months of age with skin, bone marrow, or liver metastasis, but they have excellent prognosis. The reason for this move is that studies that come out of Europe use a different classification system and North American uses a different system. So now INRG is actually a combination. Both North America and Europe has agreed to use the same classification.

This pie chart actually shows the risk stratification of neuroblastoma. Once a neuroblastoma patient gets diagnosed, it’s stratified into low, intermediate, or high risk. Oops, I’m sorry. Based on the patient’s age: age less than 18 months is good, favorable histology is good, stage 1 and 2 is relatively favorable compared to 3 and 4, N-MYC, which is a transcription factor gene amplification status. If you don’t have amplification, that is good. You have ploidy, which is a DNA content. One or less is bad, more than one is good. And then you have some genetic changes on chromosome 1p and 11q. If you don’t have that, this is good.

Based on all these factors, Children’s Oncology Group and international experts would assign neuroblastoma patient either a low risk stage, which is about 30 percent of the patients; intermediate risk, which is about 15 percent; and 55 percent of the patients, who present with actually high risk neuroblastoma. This is actually the biggest problem with neuroblastoma, that most of the patients that you see in clinic, they already have 20 bone mets, bone marrow disease, multiple lymph nodes involved. That's why sometimes local approach is just not enough. As you can see here, neuroblastoma accounts for 15 percent of mortality even though it accounts for only 8 percent of kids with cancer, so double for its incidents.
And this actually shows, based on the previously described risk stratification, if you have neuroblastoma with low risk, you have an excellent survival. Intermediate risk, almost similar survival with little bit more aggressive therapy, local as well as systemic therapy. And then you have the high risk. Despite multi-agent aggressive chemotherapy, bone marrow transplant, surgical resection, local radiation, you have not much to show for. And so this is where all our efforts need to go in. I think most of the neuroblastoma researchers would focus their attention into the high-risk patients to improve their outcomes.

And this slide actually shows the evolution of treatment over the last 30, 35 years for neuroblastoma patients, where we started with first three cycles. Now which have moved to high, multi-agent chemotherapy, and indication includes between five to six cycles, based on what protocol you are on. The chemotherapy agents that we use are vincristine, doxorubicin, Cytoxan, cisplatin, etoposide. So chemotherapy is not very different than what you guys are familiar with, and every cycle is given every 21 days. In the ‘90s, the role of BMT was better defined. In a randomized trial done by Kate Matthay, we showed that BMT actually improves outcome. So BMT, bone marrow transplant, autologous bone marrow transplant, not allogenic, autologous bone marrow transplant became the standard of care for neuroblastoma. They would get chemotherapy, surgical resection, local radiation, and a bone marrow transplant.

And the last thing I should say, in the 2000s, the role of cis-retinoic acid was better defined in a randomized trial, and so cis-retinoic acid also became the standard of care. So after patients finish that, they will be on oral Accutane for six
cycles. With all that being done, the outcome barely budged anything. I think from 20%, 25%, it moved to 36%, but not by much. This is when actually the onset in early trials from dinutuximab, which is also known formerly as chimeric 14.18, came along. This really was the much needed help the neuroblastoma community needed.

So to talk about neuroblastoma and its immunogenicity— neuroblastoma compared to an adult tumor. I think most of the centers now are doing some form of sequencing. Like foundation medicine or whatever your program is doing, like, if you look at a pancreatic or a lung cancer and you have 120 melanoma with 200 mutation neuroblastoma, you’re talking 15, 15 mutations. So the sarcoma is the same story. Pediatric tumors in general have less than 28 mutations. Neuroblastoma is even fewer than that. So when you have very few somatic mutations, the tumor is less immunogenic. And on top of that, you have young kids whose immune systems are not very robust. So it really makes for a very poorly immunogenic tumor.

And on top of that, neuroblastoma is unfortunately a clever tumor and it actually secretes various substances, which helps them hide that HLA antigen and hide them from adhesion molecules, as well as secreting some substance, which kills T and NK cells and also recruits local macrophages, which helps them kill lymphocytes. Overall, if you look at this, this actually makes neuroblastoma a very poor target tumor for immunogenic therapy. So then you say, “Well, why are we trying immunotherapy in neuroblastoma?” So the silver lining is the GD2, which is a surface carbohydrate antigen that is present in 99 percent of
neuroblastoma. It is present in newly diagnosed as well as relapsed tumors, and very uniformly and very densely expressed antigen. And it is so closely related to surface, it is not T cell dependent, as people thought in the late ’80s in LSU and others at San Diego, who thought that this might be a good target to try.

And I think more than anything else, this was a desperate attempt because at that time, all these chemo and things, nothing was working. So they said, “Well, we have to try something different.” And again, I think this actually speaks to the history of immunotherapy in general. For the last 40 years, people have been doing this long enough. They know immunotherapy is like this. Every 20 years something comes up and people get all excited, and it’s like, oh, we’re promising, not delivering much. But I think the last 10 years have been different. I think the last 10 years, when you have the genetically modified molecules, a newer way of treating, I think dinutuximab is just the first example. Everybody knows about CAR therapy for leukemia, and all the PD-1 and CTLA-4 is another for melanoma. So now you can see that there are agents which actually have right targets. This is where I think all the focus for neuroblastoma tends to be for GD2.

This slide actually shows various targets or various ways neuroblastoma can be attacked using immunotherapy. And, again, a busy slide and very small to read, but I think you can see these pink dots are the GD2 receptors, which are densely and very nicely expressed on neuroblastoma cells. Those chimeric antibodies then attach to them, and it actually -- it just labels them that this is where the GD2 antigens are and this is the neuroblastoma cells. This
combination actually recruits your own normal immune cells. It recruits lymphocytes, it recruits neutrophils, it recruits macrophages and ultimately helps them destroy it. It’s known as antibody-dependent cellular cytotoxicity, ADCC, which is the predominant mechanism of action for dinutuximab.

And then there are other approaches people have been using: CAR therapy for neuroblastoma, NK cell therapy for neuroblastoma, and some vaccines. So people have been trying various approaches, and the most predominant and the most approved and proven option is the anti GD2 therapy. This slide, thanks to Alice Yu who sent me a few of her slides for this presentation, showing the neuroblastoma staining with a dense population of neuroblastoma with the GD2 staining. As we said earlier, GD2 is expressed on 99 percent of neuroblastoma and the GD2 is also expressed in some normal cells. And we’ll talk about what leads to some troubles, skin as well as peripheral nerves and brain tissue. Neuroblastoma is also expressed on other tumors actually. The other tumors that you see neuroblastoma on is melanoma, osteosarcoma, and on some brain tumors, as well as some soft tissue sarcomas. People are actually starting some early phased trials in those tumors.

This cartoon just shows various generations, various iterations of the first generation anti-GD2 molecules. The monoclonal 14G2a is not being used anymore. This was the first one designed. This one, which you probably might be familiar with, especially if you have a team from New York here, 3F8. Sloan Kettering discovered this—Nai-Kong Chang and his team, and I think they have been using this for close to a couple of decades. It’s a murine 14.18 antibody and
has a short half-life of about 18 hours. The current drug that was just recently approved, dinutuximab, is shown here in right. It’s actually genetically modified with a variable region from mice and constant region from human, and has a longer half-life of 66 hours.

We're talking about mechanism of action of dinutuximab. I think we covered some of that. It’s an IgG1 chimeric monoclonal antibody, and it actually targets cell surface, carbohydrate receptor GD2 present in neuroblastoma, as well as peripheral nerves It attaches to GD2 and ultimately labels it so the normal immune cells, lymphocytes, neutrophils, and macrophages can come there and help kill neuroblastoma. It also works by activating complement and fixing complement by complement-dependent cytotoxicity, which is actually a minor effect for chimeric 14.18. This agent is also given with other immunomodulatory agents to enhance its ADCC, and the most commonly used are GM-CSF and IL-2.

This cartoon just shows the surface expression of GD2 in the chimeric 14.18, the murine part with human component. And so going a little bit deeper into the mechanism of action and how it actually works and creates the good as well as the bad effect, the ability of osteosarcoma to actually activate complement, which is a minor effect for killing tumors, actually leads to complement activation and is responsible for its major side effect, pain. Pain is a result of complement activation. Knowing that researchers at various institutions have been trying to navigate that and circumvent that, and I think the group at St. Jude’s have designed a humanized next generation chimeric 14.18, which
actually has a clever generic modification in switching the lysine molecule to alanine to actually create a molecule that actually does not activate complement, and there is less pain. In a comparative trial, it showed that it is not painless, but definitely there is less pain when you’re used to the humanized molecule.

This is in the early stage of development. Ultimately, these drugs will come along and make the therapy more manageable, but the approved agent dinutuximab is a chimeric, and unfortunately, it does cause pain to the patients as soon as they start receiving it. When you use the humanized molecule and when you actually do not activate the complement, it doesn’t mean that it doesn’t work, because complement activation is only a very minor effect of the drug. So in a comparative efficacy, it’s still very effective. That is probably the future’s way of going relatively with less pain and the same efficacy.

This just talks about the anti-GD2 and specifically trials focusing on chimeric 14.18, now known as dinutuximab. As you can see, the IND was actually filed before dinutuximab. This is how hard it is to develop drugs for pediatrics. If you think about neuroblastoma, and if you have 800 new tumors and half of them are high risk, which are 400, and then you cure 35, 40 percent, you are left with 1300 odd patients. And no company wants to develop a drug for 300 patients. That is the reality that’s shown here. It took them this many years to actually do the first phase I trial in '91, ultimately phase II trial. This is all single-handedly the perseverance of LSU and UCSD, who actually championed this drug in 2000, where after convincing so many different and talking to so many companies. As you can see, the list goes on.
This is her favorite slide. Even though phase II has shown activity in solid tumors, solid masses, neuroblastoma, which has relapsed with solid masses, in phase II trial, she has shown activity. No company wanted to take this drug on. And so finally she went to the Biopharmaceutical Branch, and under the orphan tumor and orphan drug category, they agreed to manufacture enough to do a phase III pivotal randomized trial which, was started in 2001.

So this slide actually is the study schema, and clearly not meant to be read. What it shows is that before you actually go to dinutuximab therapy, the patient has to receive this much therapy. As we talked about, all the six cycles of chemotherapy, surgery, bone marrow transplant, radiation, and only patients who have either very minimal disease or no disease. These are the best responders. Then they would go and receive immunotherapy. The goal of immunotherapy for initial indication is to prevent relapse, not to treat disease. We’ll talk about some of the trials, which in a relapse setting that we have been doing. This first trial, which ultimately led to FDA approval was preventing relapse.

Once the patients have gone through those, and were lucky enough to make it at the end, they will get randomized to this trial, which LSU chaired and Children’s Oncology Group ran ANBL0032. Here you have a standard arm of retinoic acid maintenance, where you get 14 days on, 14 days off, six months of therapy, or you get retinoic acid with chimeric 14.18 and GM-CSF for cycle one, three, and five, shown in yellow. Or you get IL-2 with chimeric and retinoic acid shown in purple here. And the last cycle is just retinoic acid, and again six months of therapy.
And so the results of this trial were striking. After all its stop and start and amendment, it’s such a toxic therapy, it really took a lot of time to convince investigators to open, convince moms to put their kid on a drug, which is causing so much pain, after a year of awful therapy, to say, “Now you are gonna get this, so you don’t relapse.” So really it took a long time to convince. But as soon as the first 226 patients and the first interim analysis was planned, the trial was stopped because, as you can see, the event free survival was almost 20 percent different. And this kind of number, 66 to 46 is not even heard of in neuroblastoma, and so the trial was stopped. Overall survival, again as you can see, is highly significant. So both event free and overall survival were significant, and ultimately the randomization was stopped and everybody was switched over to the chimeric arm.

Unfortunately, as it happens with cancer, as you know, this is the slide from a very recent update where you can see the same 226 patients. The curves have actually come closer. So there are some late relapses on the immunotherapy arm, and so the event free survival has become statistically non-significant, even though clinically it is significant. And this would be important because we’ll talk about a relapse trial and see why this is important. At the same time, there were some late relapses, which was really disheartening to a lot of people in the neuroblastoma community, but that’s a fact. Ultimately with these results, the FDA did approve dinutuximab for initial therapy of high-risk neuroblastoma in maintenance to prevent relapse in March 2015. In August,
EMA, the European Medical Agency, also followed suit and approved for the similar indication, dinutuximab for the similar indication.

And so far what data that we showed was for approved indication in original trial. From here what we’re going to talk about is the newer approaches using the same drug in immunotherapy for different indication. So this is the trial that I run at COG, which is a phase II trial for relapse and refractory neuroblastoma. First relapse refractory neuroblastoma—people who have actually gone through all the treatment, including chimeric antibody, if they feel they are eligible for this phase II trial. Randomized Arm A received irinotecan, temozolomide with mTor inhibitor temsirolimus, and Arm B is irinotecan, temozolomide with dinutuximab cycles given every 21 days, and total 17 cycles allowed, which makes it for a one-year therapy. In this, one noticeable absence is IL-2; it has only used dinutuximab with GM-CSF, no IL-2 in this trial compared to the previous trial.

And again, same story repeats itself. We just had our first interim analysis and only 36 patients in both arms, but we needed just three responses in order for the trial to continue. For the trial’s primary endpoint, we only needed seven responses. Within the first interim analysis in only half the patients, we showed that Arm A, which is the temsirolimus arm, had only 5.5 percent responses, while 47 percent response for (undecipherable) neuroblastoma. It is again early data and very few patients, so please keep that caveat in mind. But this trial was actually stopped and I think it's going to -- we in process of talking to CTEP and FDA and others to reopen the trial as a single arm trial with only Arm B, and
getting more immune correlates and trying to understand why these drugs work so well even in a relapse setting.

It just shows the event free survival with Arm B and Arm A, highly statistically significant. Similarly, overall survival, clinically very significant even though it’s a small number, they are not statistically significant. This actually talks about the Arm B, the chimeric arm and the eight patients who actually responded and saw the things that I wanted to highlight. It actually just shows here that among the eight patients who responded, there were patients who actually had relapsed disease or they had refractory disease. By refractory you mean, and the study definition meant, you have given at least five high-dose chemotherapy cycles in patients that has only stable disease or worse, and they have not had any RECIST-measurable response. Patients obviously who progressed or relapsed were in there, and both types of patients actually responded.

Similarly, patients who had measurable disease, which is like CT and MRI measured disease versus only on MIBG are bone or bone marrow disease, and both patients, both kind of patients actually responded. And again, this is a very heartening and encouraging slide where it actually points that patients who had prior exposure also responded. So in other words, these were the patients who were on the original trial. They responded. Some of them were the late events that we just talked about and those enrolled in this trial, and they still had response. And so this, we are hoping we can really capture this and ultimately help these patients, even when they relapse because we know from animal studies that GD2 does not down regulate. So even when you have
neuroblastoma patients who relapse, they still have expression of GD2 at a very high degree, and I think there is no -- at least so far we are not seeing any resistant to dinutuximab even in the setting of relapse, and that is a very encouraging sign.

Another very important thing here to point out is all these responses are very long-lasting. The first response is now going to 22 months, which for neuroblastoma patients it’s considered significant. Anything more than six months is considered significant. And all these patients who have responded, all eight of them have not lost their best response. So if they are in PR, hey continue to be PR or better, and if they are in CR, they have been in CR. So that is really an exciting -- and this is, again, this is unpublished data. This is the first time we are presenting this, and I think ultimately we are really excited to open this trial again, to open for more patients.

And again, the next few slides and very last few slides, I want to talk about some of the other immunotherapy approaches that investigators are using besides using the chimeric GD2. So the first two trials here enlisted are using the same molecule that we just talked about in the trials that we discussed, but Europe also has the similar trials ongoing right now. So Europe is doing the similar trials as we are doing. We have the 3F8, which is the murine 14.18 molecules and Sloan Kettering has all these trials in varying combinations. They are using that drug with NK cell, post transplant and others and using this. And now they also have humanized 3F8. So they have also moved on just like saying St. Jude’s really humanize their molecule.
St. Jude’s, as we talked about, has the humanized 14.18, and the one with the mutation, so it causes less pain. They have trials ongoing for neuroblastoma, as well as for other tumors like osteosarcoma and melanoma in children. The first CAR therapy is also ongoing for neuroblastoma at Baylor School of Medicine. And again, there are two vaccine trials: one at Baylor with oral Cytoxan, and the second is Memorial Sloan Kettering, using bivalent vaccine. So not only there are chimeric antibody in dinutuximab, which is an approved therapy being used for neuroblastoma, but there are several other versions of second and third generation immunotherapy approach people are using to really prove the outcomes of these really poor-risk patients.

This is my summary slide before we move on to my other speakers. Just a take-home message for you guys, that survival for high-risk neuroblastoma, despite aggressive therapy, chemotherapy, surgery or transplant, radiation, still remains poor and innovative biologics therapy and immunotherapy is really needed. Dinutuximab is the first approved agent approved for first in the initial therapy of neuroblastoma in maintenance to prevent relapse. Early data, even though this is a non-approved indication, looks very encouraging for relapsed patient using dinutuximab with chemotherapy.

However, the point to remember is dinutuximab therapy has some very serious, predictable but serious side effect, and one that requires very careful monitoring. One well-designed, interprofessional approach would really help the patient population, and it is really needed in general for pediatric oncology. But this is a tumor and this is a therapy where if you’re gonna have a multidisciplinary
team, this is the therapy that you want to use it for. And that is one of the reasons we chose this symposium in the format that we chose, and I think this is a very good example how we can use the professionals to use them. And so with this, I want to hand over the mike to Erika who is going to take you through the administration and side effect profile.

**DR. ERIKA MORA:** Thank you. Before I begin, I just want to say for the remainder of the presentation, my colleagues and I will be going back and forth presenting some slides. We’ll try to do it in a non-distracting way, but there will be a little bit of back and forth. So Dr. Mody did a great job explaining why it’s very important to utilize immunotherapy and neuroblastoma, and I am tasked with bringing everybody down to earth to talk about how toxic it can be and how you can work to prevent those side effects.

So the FDA has given two black box warnings to dinutuximab. The first one is for pain, as he discussed. Monoclonal antibody works by targeting GD2 on the cell surface receptors, and GD2 is also expressed on peripheral nerves, and so pain is very predictable with this medication. It’s very severe. There’s a neuropathic component of that and so we’ll talk about that further. Along with that, infusion-related reactions are common. It’s a chimeric human/mouse monoclonal antibody, so same types of infusion related hypersensitivity or anaphylactic reactions you see with other monoclonal antibodies can be seen with dinutuximab.

And then finally there are some other serious side effects that we see with dinutuximab, but we also see with some of the concomitant therapies. And so
hypotension, we’ll talk about how we administer continuous infusion opioids with the dinutuximab so that can be compounded by opioid therapy. Some of the other immunotherapy that’s given with dinutuximab can cause hypotension. Capillary leak is a particularly severe side effect that can occur and so we’ll talk about that as well, but you can see it with dinutuximab and you can also see it predominantly with IL-2. That first study that Dr. Mody talked about where you give them both together, capillary leak is a very severe side effect that can occur. And then finally fever. This medication causes lots of fevers and our patients commonly experience fevers when they receive this antibody and so that’s another thing that we see frequently.

So this is, again, a slide with a lot of small writing on it, but this just shows the patient population from the LSU study that Dr. Mody talked about at the beginning and some of the side effects that we saw with that. And so neuropathic pain, which I’ve alluded to already, occurred in 52 percent of patients who were already receiving continuous infusion opioids. Hypotension occurred as well in 18 percent of patients. Again, this can be exacerbated by giving opioids. Fever without neutropenia occurred in almost 40 percent of patients. I would say we see at least that much in the patients that we have treated so far at our institution. Fever is very common. And the acute capillary leak syndrome occurred in a quarter of patients, and we’ll explain which cycles that happen more commonly on the next slide. Hypersensitivity reactions. Again, this is a monoclonal antibody. And then some lab abnormalities, specifically hyponatremia and hypokalemia. Those are seen fairly common, likely due to
some fluid shifts in patients that are experiencing capillary leak, and then also some elevations of LFTs.

So again, this is the same patient population. This is just looking at some of those more severe side effects broken out by cycle. And so the first one, pain, which we’ll focus on the most, it does look that it may trend to less pain the more a patient is exposed to this medication. And what we don’t know is if that trend is due to the treatment team becoming better at treating that patient’s pain and learning what works for that patient over time and then just prospectively managing it more appropriately, or if there are some component of tachyphylaxis. And so that’s some things that scientists are trying to think through now and to see, you know, maybe if there’s a tachyphylaxis component. Particularly in Dr. Mody’s study, where there were 17 cycles of the dinutuximab, it wasn’t uncommon for the patients to have less pain as they got further through the therapy.

The next two hypersensitivity reactions in capillary leak, again I’ve highlighted cycles two and four. If you remember from the previous slides, those are the cycles where the dinutuximab was given with the IL-2, and so these side effects were much more common when given concomitantly with IL-2. And then a similar slide—this is just from the patient population that Dr. Mody presented from the 1221 trial. So remember, these are patients with relapsed refractory disease, and Arm B was the group that received the dinutuximab. Again, 50 percent of these patients had severe grade 3 or grade 4 pain and that’s going to be despite receiving continuous infusion opioids. Anaphylaxis rates were at zero.
We'll kind of talk about some premeds, but we do pre-medicate these patients before they receive their medication.

F&N positive blood cultures were at zero in this trial. However, there were some patients that had hypotension as well as hypoxia and dyspnea. And I want to just focus for a second on this number right here because of one thing that we learned specifically with this trial. In the past, we had treated patients that had very minimal disease or were in complete remission. In this trial, it was a relapse refractory trial. And so there were patients that had pulmonary mets or lung disease, or patients that had large abdomens and small lung volumes. And in those patients when they started to develop capillary leak, their hypoxia and dyspnea could get severe very quickly. So those are patients that really require a lot of monitoring, especially in those situations where they start to develop capillary leak because they can have respiratory compromise. Again, just some lab abnormalities highlighted here.

So focusing on the pain, the pain with dinutuximab is severe, as you can tell. Despite continuous infusion opioids, half of the patients will have grade 3 or grade 4 pain. It’s acute. It starts right when you start the infusion of the dinutuximab. It’s continuous throughout the infusion of the dinutuximab. For a lot of patients, it does resolve when the dinutuximab infusion is turned off, and so most of the time you’re able to wean off of the opioid before the next day’s infusion starts, but we have found that that’s not always the case and so the vignette of the mother that you’ll hear talk later, her child definitely had pain that
did persist after we turned off the dinutuximab, and so every patient responds a little bit differently.

As far as some barriers to adequate pain management, I just want to focus that these are young patients and so they’re toddlers. They can’t tell you what hurts, they can’t tell you what makes it feel better. So a lot of times it’s really difficult, not only for the patient and their family members to see their kid going through this pain, but it’s also hard for the team to understand when they’re in pain, are they just agitated, are they anxious, is it true pain, where is the pain, and what’s going to work the best. Additionally, we use different pain scales for children and trying to figure out which one works the best is difficult for young children. And so there’s a lot of barriers to really adequately identifying pain and treating pain in this patient population.

And then finally, I want to just focus for a second on capillary leak. So again, this is another side effect that can occur with dinutuximab that can be really severe. Capillary leak, like we showed with the different cycles of LSU study, is definitely more common when patients are concomitantly receiving IL-2, and so giving it with other therapies that can cause capillary leak increases your risk for developing it. However, the severity can also be exacerbated by the continuous infusion opioids, which can cause some hypoventilation and help lead to some more respiratory compromise. One thing that we’ve learned at our institution and I think that is fairly well documented is that anemia is also a coexisting risk factor for capillary leak. Adequately transfusioning patients if they are anemic for us -- our transfusion thresholds are typically hemoglobins of
seven or eight, but on this protocol they really want your hemoglobin above 10 if you start developing capillary leaks. Utilizing packed red blood cell transfusions, if necessary to make sure you’re having the oxygen delivery.

Again, there is an increased risk with mediastinal disease, and then just the balance of managing intravascular depletion and hypotension. So usually the go to would be to give IV fluids, and that still is recommended to acutely manage the hypotension. But you just don’t want to flood the lungs in somebody that’s become leaky and cause more respiratory compromise. And so it’s a delicate balance. I talked about red blood cell transfusion. You can also utilize albumin if the patient has an albumin less than three, and then vasopressors can be used. We’ve had that situation at our hospital where we’ve had to give somebody vasopressors for capillary leak. And then I just want to highlight, it’s not on the slide, but absolutely you should stop the infusion of the dinutuximab or the IL-2 if somebody is getting into trouble with capillary leak, so that you can support them through it with some of these other therapies.

In a second I’ll turn it over to Rhonda. So before we go through our patient case, just how you administer dinutuximab. So we talked about some of the side effects. We start out with an IV bolus of normal saline, and then they get their opioid loading dose. We deliver all of this through our PCA. We preferentially use morphine, but we have had patients receive hydromorphone. Then they get Tylenol and Benadryl. That’s prior to infusion because it is a monoclonal antibody and there are infusion-related reactions. We have learned over time the importance of initiating Gabapentin prior to them coming in for their dinutuximab
infusion, so we titrate that up over a three-day period to their full dose. And so all of these things get started, and then once they get their loading dose of their morphine or Dilaudid, we start a continuous infusion of their morphine or Dilaudid. So that it’s all on-board and those receptors are saturated, so once the dinutuximab starts, we hopefully have some adequate pain control at that point.

As far as administering the dinutuximab, it’s similar to other monoclonal antibodies. You ramp up the rate. You start at what is considered half rate or 0.875 mg/m². That goes for 30 minutes. And then after that, you go up to the full rate, which is 1.75/m²/hr. And then if you do that, you do not need to slow down the infusion or stop the infusion. For most hospitals depending on how it’s compounded, the infusion would end in 10 to 11 hours approximately. With this medication, the way it was studied, you have up to 20 hours to give a dose. And if that dose it not finished within the 20 hours, you would stop it and not give the rest of it, and then the next day would start after that. So it’s four days in a row for each cycle. Typically up to 10 to 11 hours for each dose, but you can slow it down for side effects up to 20 hours. Now I’m going to give it over to Rhonda.

**MS. RHONDA MCDougall:** Hi. Hopefully, what I’m going to do is review several patient cases for you, so that you can see or it will demonstrate our process of progression, and how we came up with a plan of how best to treat these patients. You will see from this, a lot of the information that Erika covered as far as side effects, how it is that we treated them initially, and how we progressed at better managing these patients.
So our first patient is a 14-month-old male who had stage IV neuroblastoma with widely metastatic disease, primarily osseous disease. He, as Dr. Mody had stated in the previous protocols, had received six cycles of induction chemotherapy and had gross total resection of his tumor. Disease evaluation following that resection showed that he had small areas of MIBG avid disease and he was graded as a very good partial response. He then underwent autologous bone marrow transplant followed by radiation to the tumor, primary tumor site, as well as the sites that were still active for positive disease after transplant. And at the time of his progression onto immunotherapy, he had a complete response and had no signs of active disease.

During the first cycle of his immunotherapy, we readily identified that there was going to be an issue as far as available lumens, venous access. He had a single-lumen Mediport, and so in order to be able to give the dinutuximab as well as the supportive care, we needed to place a peripheral ID on this child. We again, started morphine both as a continuous infusion as well as bolus. But in spite of our best efforts, he had significant intractable pain, which required additional doses of morphine as well as slowing down of the dinutuximab rate. He also had complications with nausea and vomiting, decreased urinary output, and weight gain, which was managed with additional IV fluids, and he was found to have anemia and we gave packed red blood cells as well.

During cycle two, again we had multiple line issues. During the course of his treatment, which would have been a week, he necessitated four different peripheral IVs because we just had difficulty maintaining that line. Again, we
started his morphine drip, adjusting it based upon what he had required in the previous cycle. He continued to have inadequate pain control with inconsolable crying and whimpering, which was very distressful for the family.

Then he went to cycle three. Again we had anticipated that we might have issues with available lumens, so at that point in time we placed a PICC line in addition to his Mediport. Again we started with utilizing continuous morphine and a PCA, based upon his previous cycles. On day one, he had significant pain. His mother was quite distressed and said, “I have never seen him in this kind of pain.” We bolused him with morphine. We also gave lorazepam for agitation. Again, in a 14-month-old, it’s difficult to know exactly what they’re experiencing. Unfortunately, we were not able to provide relief for this child and the mother elected to withdraw this child from protocol. So they stopped treatment after three cycles.

The downward effect of that or the downtrend effect, as many of you know or at least in the pediatric population, many of our parents talk to each other and talk about treatment, what their child is experiencing. So this mother relayed this information to many other families and there were at least a couple of families that made the decision that they didn’t want to proceed with this therapy due to his response. We’re going to go back to Erika.

DR. ERIKA MORA: I’m going to keep popping back up here. So just to summarize with this patient case, there were some identified issues that we as a group recognized with this first vignette. The first one, we do not think that the parent was appropriately counseled about expectations prospectively, which led
to some tension in the room when the patient did have these side effects. Clearly when he was in pain, we were having open dialogue with her and kind of explaining what was going on and trying to get ahead of that. But one thing that we did learn was maybe trying to set that up prospectively, so they knew what to expect going into the therapy versus reacting to that pain.

The patient did have inadequate pain control, and there were some varied approaches between some of the teams that were taking care of this patient. At this time, our main teams that were involved in treatment of these patients were the peds hematology and oncology service, as well as our acute pain service. And our acute pain service is more adapt to treating post-op pain and relying on boluses and demand doses, and so you may not have noticed but the PCA settings per cycle for this patient didn’t really change a whole lot. When he got into pain, they would come in and try to bolus him, and it was more reactive.

I think what we learned from that was to be more proactive and have more pain control delivered through a continuous approach, because the infusion is continuous. Neither approach is right or wrong, but there was just differences of opinions at that time. And inadequate venous access is continually a problem when a patient is getting into trouble or having pain or needing supportive care, and you can’t give it because there’s not appropriate lines. I’m sure you guys have all had patients in that situation. And so again, trying to be proactive with that. These are kind of some of the things we learned from him. Rhonda will talk through another case.
MS. RHONDA MCDougall: Case number two is a 24-month-old female, who also had stage IV neuroblastoma with widely metastatic disease, primarily osseous disease. She also received five cycles of induction chemotherapy followed by gross resection. Fortunately at the time of gross resection, she was in complete remission, so she progressed onto autologous bone marrow transplant as well as radiation to the primary tumor bed. At the time she was going to move on to immunotherapy, she continued to remain in remission.

During cycle one, we had at that point in time already established that we were going to start patients preemptively on Gabapentin, in order to help with that neuropathic pain. So the patient is gradually titrated up to 10 mg/kg over three days prior to their admission. She, fortunately, did fairly well and her pain was pretty well controlled with what we had identified would be standard continuous morphine. At this point in time, we had changed in our clinical practice to have it be nurse-controlled anesthesia, so that the nurse actually had control over whether the child was getting bolused morphine. She had good pain management. She also developed fevers, which did not escalate to anything else, so we just observed and treated those appropriately. She had intermittent mild hypotension, but it did not require or necessitate any interruption, and she was able to complete the cycle.

During cycle two, her pain was well controlled on the above, the previous cycle’s management with gabapentin, with the addition of gabapentin as well as continuous and bolused morphine. She developed hypotension during only one
episode with blood pressure, a systolic blood pressure into the 60s. We paused the infusion of the dinutuximab and gave IV fluids. She was able to receive the rest of the infusions without any other problems. She did develop fevers up to 41 degrees Celsius, so we did a complete septic workup. She was non-neutropenic, so we started cefepime empirically and all cultures came back negative.

So for cycle three, again, at this point in time, we had pretty much resolved or had been successful in managing her pain. Although she continued to have daily fevers, again septic workup was done. All cultures were negative and she was able to complete that cycle. Unfortunately though, during cycle four she developed fluid refractory hypotension, along with bilateral pedal edema and delayed capillary refill. So both the IL-2, because she was receiving IL-2 in cycle four, and the dinutuximab were placed on hold. And in spite of fluid boluses, she continued to be hypotensive and also anuria, so we elected to transfer her to the peds ICU for closer monitoring. Also, eventually, she was started on pressors. When she became hemodynamically stable and she had been off pressors for greater than 24 hours, we resumed the dinutuximab at 50 percent infusion rate and she was able to complete the cycle, although we continued to hold the IL-2.

**DR. ERIKA MORA:** So identified issues for this second patient case, as Rhonda showed, we actually did a pretty good job with her pain. She tolerated the therapy fairly well until cycle four, and then cycle four everything went downhill, and she ended up in the ICU on vasopressor support. So, drastic improvement in pain control with the prospective addition of gabapentin. However, balancing that fine line of managing capillary leak on the floor is very
difficult. That was something that we got firsthand experience with. As far as plan for how do you reinitiate therapy in a patient who is receiving epinephrine in the PICU.

When you restart it, when you take off the epinephrine? Which one do you restart? What rate do you start? Do you give both or do you hold the IL-2? So these are all discussions and issues that we had to kind of work through and talk to the study coordinator to figure out how to best take care of this patient. For the ongoing consensus management for persistent fevers, do you start antibiotics? How long do you keep antibiotics on? When are you fairly certain that the reason the patient is having fevers is because of the medication and not because of an infection?

So kind of going over all of those identified areas of improvement, we met multiple times with the ped hematology/oncology group and several of the other groups that help to take care of these patients. The one thing that we just absolutely decided is that we needed to have a standardized process when these patients came in, where all of the teams were on the same page. It was written out. It was easy for nurses, overnight staff, everybody to access and to follow our protocols. Everybody bought into our protocols and then they were approved. We wrote a clinical practice guideline for how to take care of these patients when they are admitted, which I'll show you a piece of. Part of that clinical practice guideline focused on pain management and making sure that we all had the same thought process for how pain management should be undertaken.
Again, it’s a guideline. We could have refractory patients that don’t follow that guideline, but at least being on the same page and initiation as far as prospective management for pain. Optimization of available lumens, we have learned that two lumens is minimum. There are some cycles where three lumens is minimum depending on compatibility between some of the medications and some of the pain regimens. If a patient were to need hydromorphone, there is less compatibility information with hydromorphone and IL-2, for example. Certainly, sometimes we even need three lumens. And then the interprofessional approach, again, we’ll talk more about this with Beth from palliative care and family-centered care. But these are huge. These patients require a lot of supportive care, and so really bringing everybody’s best expertise to the table has really been something that has helped us tremendously with these patients.

Going back to our clinical practice guideline, the document that we created-- this slide goes over some of the things that it includes. One is a pre-immunotherapy multidisciplinary clinic visit. Again, if you go back to patient one, we just felt that maybe we didn’t prospectively set them up with enough education to know what to expect. Beth will talk more about what things are included in that clinic visit, but that’s included in our clinical practice guideline. Appropriate supportive care. So again, our first patient did not get gabapentin prospectively. It’s something that we learned over time that if you look at the data, it seems pretty clear. Regardless of continuous infusion opioids, half of the patients will experience severe pain.
It makes sense that it's a neuropathic pain. Maybe opioids are not the best medication to treat this, and so we have really learned over time that initiating gabapentin upfront is huge and so that is now standard for us. We have that outlined in our clinical practice guideline: what dose to start, how to titrate it up, and how to titrate it down between cycles. I think that there are some centers that just keep it on between cycles. I don't think there is a right or wrong approach, but we kind of outline what our approach is in our guideline.

Again, predetermined guidelines for acute pain management and escalation, we have determined specific workflows for initiation of the PCA, if it's cycle one. So kind of starting from scratch, versus subsequent cycles, and making sure that we are taking into account what the patient required on the previous admissions, is what worked well. Documenting that consistently, so that when they come back in the next time we’re not reinventing the wheel. And so all of that is outlined, really, really focusing on a proactive, prospective approach versus the reactive approach, which we learned the hard way doesn’t work. And then algorithms for treatment of hypotension and capillary leak. It’s just important to have these easily ready for the nurse to be able to grab it, and know what to do in the situation instead of trying to log in and sift through a 400-page protocol to determine what the right thing is. We try to be proactive and include that, as well.

This is just a snapshot example of our opioid nomogram. It only covers the top part of our flow sheet. But just to give you guys an idea, the first box kind of talks about our loading dose and what we would use. Then it separates out
whether it’s course one or subsequent courses for our PCA, how we determine our demand doses, how we determine our continuous infusion doses, how we document it in the chart, who documents it, et cetera. The bottom part, which you can’t see, it even goes so far as to say when you reevaluate your patient: If they’re hitting their button more than one time an hour, how you calculate what changes to do in the continuous infusion, who is responsible for calling who, who is responsible for evaluating the patient. Everything is laid out and all of the teams that play a role in that process are educated on this and buy into this method. Nobody is guessing or assuming that somebody is doing something, and then it gets missed.

**MS. ELIZABETH HOLLENKAMP:** For the sake of time, I’ll try to move through a few of these slides, because they’re probably not new concepts to most of you. But based on our identified areas of improvement, which Erika talked about, we recognize the importance of interprofessional approach and family-centered care. There is now an institutional commitment to this partnership, recognizing that the family is really part of the team. The goal is to foster communication between the families and providers, and to facilitate quality patient care that addresses the physical and psychosocial needs of our patients and families.

So research has long suggested that interprofessional collaboration really improves coordination, communication, and ultimately the quality and safety of patient care. This kind of care is demonstrated based on the five principles displayed here. I would emphasize the importance of effective communication,
recognizing this is not just an exchange of information. It’s really about understanding the emotions and the intention behind the information. This is the glue to help you deepen your connection with others, to help you improve teamwork, decision-making, and problem solving.

So to execute interprofessional care and effective communication, we’ve utilized the role of champions. We’ve identified passionate learners, who are among the disciplines in our institution, who are well-versed in our clinical practice guideline, and obviously committed to improving patient outcomes. Like Erika briefly mentioned, we meet prior to the initiation of therapy. These champions come together. We provide the patient and family education regarding the therapy and the additional resources available to them during their admission. This is all done in the outpatient setting prior to their initial admission.

These champions consist of representatives from our pediatric hematology/oncology team. Often it’s a nurse practitioner, a bedside nurse, and the pharmacist. In addition, there’s a representative for the palliative care team, acute pain service, and Child Life specialist team. Additionally, the social worker, spiritual care providers, and PICU colleagues are also notified of an anticipated admission. And then throughout the other inpatient cycles, the champions continue to collaborate and reevaluate our CPG. Now I’m going to send it over to Rhonda to talk about our third case.

**MS. RHONDA MCDougall:** I’m going to briefly discuss this for the sake of time. Basically you’re going to see how we’ve kind of come full circle and how, hopefully, we’ve made headway into treating these patients and can continue to
So our last patient is a three-year-old, a male who also had stage IV neuroblastoma with extensive metastatic disease. He also was treated with six cycles of chemotherapy and underwent surgical resection following that. Unfortunately, at the time of his surgery, his pathology revealed that he had positive margins and only had about five percent of tumor necrosis. Ninety-five percent of his tumor was active.

So following that induction chemotherapy, disease evaluation showed that he still had significant MIBG avid in his bone marrow. So the decision at that time, given his age and behavioral issues with this particular patient, was that he wasn't a candidate for MIBG therapy or autologous bone marrow transplant. He was enrolled onto the newer study that Dr. Mody talked about, which fortunately he was randomized to the regimen B cycle or the regimen B. So he got 17 cycles of regimen B, which included the standard chemotherapy of temozolomide and irinotecan for five days, as well as the addition of dinutuximab and GM-CSF.

He experienced multiple adverse events during this, as far as he had pain in all 17 cycles. He had fever in seven of those cycles, hypotension in four of those cycles, nausea and vomiting in three, hypoxia in three cycles, and rash in two. So you can see that we pretty much had the same profile as what was reported when Erika talked about side effects. The good news is after the completion of these 17 cycles, he was in complete remission and remains so currently. Despite the family’s hesitancy and anxiety prior to starting this therapy, and after 17 cycles of therapy that obviously had significant side effects including
pain, the mom’s reply to us was, “Do we have to stop this drug? Why can’t we just keep on giving it to him? He responded so well to it.” So it just goes to show how these parents can appreciate that if they stay the course and follow this, that there hopefully will be success. Thank you.

**DR. ERIKA MORA:** I just want to quickly highlight. We’ve talked about a lot of pharmacologic ways to intervene with these patients and provide supportive care. There are obviously lots of non-pharmacologic ways, as well. Again, these patients are very young, so the one that we have benefited from the most is Child Life. Having them involved before they get admitted, trying to learn what the patient likes and what is a good distraction for them, has been huge. So we’ve really utilized our Child Life team to come and do distraction techniques, and play games with our patients and really get their mind off of the pain.

Additionally, another learning point, expect the unexpected as you can tell from the three patients we talked about. They were all very different, and even between cycles, potentially were very different. And so for us, we have our guideline and we have our standard, you know, morphine PCA or Dilaudid PCA that we utilize upfront and kind of we cross our fingers and hope that that’s gonna be effective for the patient. But when we have that pre-clinic meeting before their first cycle, we do talk to the families about plan B and plan C if those don’t work. And so for us, our plan B is a lidocaine infusion if the opioids are not working. That would require a transfer to the PICU. So we talk to the families before they come in. And say transferring to the PICU is something that could happen in order for us to provide adequate pain relief. It doesn’t necessarily mean that your
son or your daughter is acutely ill or decompensating, it just provides us a safer place to give different types of medications and more monitoring.

So we talk them through that process so that they are aware that that could happen. Other institutions could switch to fentanyl. I know that there are some other places that have been looking at using ketamine or propofol, and so these are all different things or techniques that have been utilized that could be your plan B or your plan C at your institution.

**MS. ELIZABETH HOLLENKAMP:** Our mission is to provide evidence-based pain and symptom management as defined in our CPG, and to reinforce an interprofessional team approach as a standard of care. This is definitely easier said than done. Our goal is to reduce inconsistent practices, improve patient comfort and compliance, and enhance team member collaboration. We are currently implementing this through a patient and family therapy guide, patient experience survey, and quarterly reviews. This is just a snapshot of our patient and family therapy guide. This is distributed during our outpatient visit prior to initiation of therapy. This educational tool is really intended to help our patients and families to better understand the treatment regimen. It highlights the medication information, the glossary of terms, the calendar and treatment of schedule, anticipated adverse effects, and the team and resources available to them.

This is a snapshot of our patient experience survey. This is also distributed to them following each cycle. Our goal is to really better understand the patients’ treatment and symptoms they experience, to identify if there are any
patient trends, and to improve patient outcomes. Unfortunately, surveys do not capture the emotions and they do not tell our patient and families stories. So we recognize the importance of going straight to the source. Now we’re going to have the opportunity to listen to a mother’s reflection as she talks about her son’s journey through the dinutuximab antibody therapy. This slide displays the eight questions that we interviewed her with, and you’re going to have a chance to listen to the audio response following each question. We first asked the mother from her point of view to please describe what this treatment was like for her.

**MOTHER:** It has been difficult. In that aspect, it’s been difficult because of trying to understand what reactions are from what. Knowing if it’s from the -- which specific medicine is causing what problem. That has been our biggest concern I think throughout this whole thing. Understanding that your child is going to be in pain and then trying to focus on the fact that that pain is going to make him better. Knowing that it’s going to help their situation and prolong their life.

**MS. ELIZABETH HOLLENKAMP:** We then asked what advice she would give other patients or families starting the treatment regimen.

**MOTHER:** The best future advice I could give somebody would be to make sure that they -- if their child is old enough, to talk with them about what kind of things they think is going to help them when they’re not feeling good. If it’s a matter of having some kind of a word or a signal, so that the parent knows what’s going on. That way if your child is in a lot of pain, there are ways for you to know that without having to pester them constantly, “Are you okay? Are in pain?”
Do you need this? Do you need that?” Making sure that your child is aware of what’s going on. To maybe have like -- I know with us, specifically we talked about when you’re going to get into that pain, what can we do to get your mind off of it? And Child Life was a great help with that as well. And just to have something already in place, so when it gets to that point and you’re like, “Okay. We talked about this. Now this is what we’re going to do to try to help you get through those steps.” I think that’s pretty important to have that kind of a thing with your child to help them get through that. And understanding if they’re old enough, that is, what it’s going to be like without scaring the heck out of them.

**MS. ELIZABETH HOLLENKAMP:** For health care providers who do not have experience with this treatment regimen, we asked her what would be helpful for them to know or to consider.

**MOTHER:** That they need to listen to the parents when the parents are telling them that there is something going on or that there is pain is going on, and communicate with the nurses, because most of the time the nurses know these kids already. And to understand, okay, we already know that this is what’s going on. We’ve tried everything before we even called you in. And for them, if they’re not sure what to do next, go in the hallway and ask somebody who does or to get advice. For them not to just pull at straws in front of the patient. Sometimes it’s best that they just go out of the room and they can think out loud or whatever they need to do. Just not in front of the patient, when the patient’s in severe pain at that very moment, you know. It’s not a good thing to see a new person
stumbling because at that point, a parent just wants somebody to help their kid and just fix them.

**MS. ELIZABETH HOLLENKAMP:** Next we asked her how did having a team approach affect her son’s care.

**MOTHER:** I think it helped tremendously. I think that with the different teams, mainly the palliative care and the acute pain care, had different things in their back pockets that they knew that could help. If one aspect of the medicine is causing a certain pain, they had other ideas of what could help relieve some of that pain. And then with Child Life stepping in as well and trying to give different ideas to the children and to the parents of what to do to try to help get through it. I think that’s just been such a blessing to have multiple people, like, having ideas. And when they’re actually communicating with each other, it’s fabulous.

**MS. ELIZABETH HOLLENKAMP:** Next we asked her what has been the most difficult part of this treatment regimen for both her and her son.

**MOTHER:** I think the most difficult part has been the fact that my son has had the extended pain and side effects after treatment had finished. We were kind of prepped that once the infusion was done, the pain would stop, and that hasn’t been our case. And knowing each child is always an individual, but -- and then honestly with some of the pain that he was experiencing and the side effects, the anxiety of having a relapse, that has been the most difficult. It’s just worrying about the relapse because of the side effects.

**MS. ELIZABETH HOLLENKAMP:** Next we asked if have there been any interventions that have made this difficult treatment regimen more tolerable.
**MOTHER:** I think in our case, having the extra different types of medicine that were available has been super helpful. So like if something isn’t working or he just needs that little extra oomph, it’s helped and that’s made it easier on him to get through it. And the fact that the nursing staff and the doctors really do take into consideration how each kid copes with everything. So where my son likes it nice and dark and quiet and not a ton of people in his room, they’re very respective of that. I think that makes everything easier when the people that are trying to help your son are actually paying attention that it is your child and that it’s, you know, not just another number or just another patient. They’re very caring, and that just makes everything easier.

**MS. ELIZABETH HOLLENKAMP:** We then asked if there were any interventions that were not done that you think would be beneficial in the future.

**MOTHER:** I don’t really think that there was anything necessarily specific that I wish would have been done other than maybe understanding the side effects of some of the other medications. I think that it’s concentrated on this is the side effects that are possible for during the chimeric or the IL-2, but it’s not really discussed all the other side effects that come with taking the other medicines, the gabapentin, the Leukine, that kind of stuff. And I think sometimes that would have been a little bit more helpful to know what to expect instead of being like, “What’s wrong with my kid?” When really there’s a good chance it’s just a side effect from one of the other medicines, as well.

**MS. ELIZABETH HOLLENKAMP:** In conclusion, we asked her if there was anything else that she would like to share with our team.
**MOTHER:** I think that you guys are doing a fabulous job with knowledge is power, and trying to put that knowledge and having everybody on the same team. I really do just think that that will keep improving as you guys go, and that it’s just going to be more and more helpful for the kids. And as more doctors are aware of this treatment, it’s just going to make it easier.

**MS. ELIZABETH HOLLENKAMP:** This mother really answered from her heart. I think that it highlights some of our successes, but also rooms for continued improvement. And I’ll let Erika take over from here.

**DR. ERIKA MORA:** So we’re going to summarize this really fast, and then we’ll go to your questions for your CE credit. In summary, Dr. Mody outlined the benefits of dinutuximab therapy and immunotherapy in neuroblastoma, and then we have also kind of illustrated a lot of the side effects in the toxicity profile. The side effects are predictable, but they are serious., so really having that team approach and a proactive approach for preventing them. Well-planned, multidisciplinary approaches are instrumental. Different concomitant therapies, as well as, progressive cycles can change the landscape of the side effects that we’re seeing with dinutuximab. In addition, the next generation or humanized anti GD2 monoclonal antibody therapies may potentially decrease some of the side effects that we’re seeing, by decreasing that complement dependent cytotoxicity. Hopefully, a lot of these side effects either are eliminated or downplayed in the future, just based off of our improvements in our technologies with these therapies.
We can go to the questions first. I think you guys have been doing the text question web based all day, so you should be familiar with this format. So the first question is, which of these statements regarding the role of dinutuximab and the treatment of high-risk neuroblastoma is the most appropriate? It should be used for all patients who have relapsed following upfront therapy; it should be given to everyone as soon as they are diagnosed; it is an approved therapy for both front-line and relapsed high-risk neuroblastoma; or it’s an approved therapy for use after chemotherapy plus surgery plus auto-transplant and radiation and the front line therapy of high-risk neuroblastoma.

Good job. So you guys were listening pretty good. I think the tricky answer here that got a few of you guys is that selection A, it should be used for outpatients who have relapsed following upfront therapy. That’s more the setting of that 1221 study that Dr. Mody is the PI for, and I think this is still experimental. The numbers look great, but it’s still just small numbers at this point in time. So I don’t think you can say that it should be used for all of these patients yet, until we get some more data. But the last one would be the one that would be the correct answer, which would be for upfront therapy for high-risk neuroblastoma. But in maintenance to prevent relapse after they have received all of those other therapies that we talked about that led to still some pretty crappy long term outcomes, you would add this immunotherapy to then.

The next question: JH is a patient with high-risk neuroblastoma who is in complete remission at time of transplant. He is now due for immunotherapy with dinutuximab, GM-CSF, and IL-2. Which of the following best describes the
mechanism of action of dinutuximab? So is it a small-molecule tyrosine kinase inhibitor that works intracellularly on the GD2 pathway to downregulate neuroblastoma cells? Is it an immunomodulatory agent that activates cellular immunity and leads to production of cytokines? Is it a monoclonal antibody against cell-surface GD2 that labels cells for immune destruction? Or a colony-stimulating factor that triggers proliferation and differentiation of hematopoietic progenitor cells?

Good. So it’s C. So the answer A, is kind of trying to trick you up, so small-molecule tyrosine kinase inhibitor. It does work on GD2, so that’s right, except GD2 is located on the cell surface, and so that’s how the monoclonal antibodies target it on the cell surface versus it being an intracellular tyrosine kinase mediated mechanism. And then the second one, an immunomodulatory agent that activates cellular immunity and leads to production of cytokines. That would be more typical of your IL-2 type of therapy.

So question three: JH has started immunotherapy and is currently receiving dinutuximab and high-dose IL-2 on cycle two, day seven. He is experiencing 8 out of 10 pain, as well as increased weight gain, tachypnea, and de-saturations into the high 80s. Which of the following interventions should not be considered? Stop dinutuximab and IL-2 infusions; continue your morphine PCA and provide supplemental oxygen; slow your dinutuximab or IL-2 infusions, continue your morphine PCA with an additional bolus of morphine for pain and provide supplemental oxygen; keep your dinutuximab and IL-2 infusions the same, bolus your morphine for pain control, as well as give a dose of lorazepam...
for presumed anxiety; or stop dinutuximab and IL-2 infusions and consult the PICU for an evaluation?

Oh, it shrinks. Oh, the last one is shrinking. That's good. So the answer is C. So what you would now want to do is keep dinutuximab /IL-2 infusions the same, bolus morphine for pain control, as well as give Ativan. And main reason for this is just in a patient who is already tachypneic and de-satting, you probably want to have some supplemental oxygen as part of your treatment plan. In addition, likely these side effects would improve if you either at least slow down the infusion or stop the infusion of the dinutuximab and the IL-2. So the first thing we would do is either slow those down or stop those completely, give supplemental oxygen, get ahead of the problem. Additionally, you could still provide opioid pain medication because the patient is in pain, but you would want some supplemental oxygen to make sure he’s not de-satting further. Whereas in selection C, it just boluses some more morphine without the supplemental oxygen and the patient looks tachypneic and de-satting. So that would be the answer we would stay away from, realizing that there are a lot of different ways to treat this patient. So there’s not one right answer.

And then the last question: All of the following are key components except for which one that should be utilized when caring for a patient receiving immunotherapy? Family-centered care, interprofessional team approach, reactive pain management, or effective communication? Good. So C, reactive pain management. I do want to emphasize that reactive pain management is likely to be part of your patient care because you will have patients that get into
pain that you need to react to. However, really what we have learned and hopefully demonstrated over time that the prospective, proactive treatment approach is something that really gets better outcomes in the long run. So that’s all for the questions. I think we will conclude with Dr. Mody doing acknowledgements.

DR. MODY: So again, I just want to acknowledge a lot of important people who actually made this talk possible. I guess the first one would be the three sitting on the stage. I just wanted to thank Erika, Rhonda, and Beth for helping me put together a very nice symposium and I hope you guys truly enjoyed or learned from it. So thanks to my colleagues. I also want to thank several other members who are not here, but part of our multidisciplinary team, including Judy, Dr. Pituch, Trish Keefer, Sandra Merkel who are part of the palliative care team or the pain team, and some of the ICU attending including Dr. Niedner, and our nursing floor, nursing team, as well as Child Life team.

And most important that we all like to think and really learn and take cues from is our patients and families. I think without their support and their desire to enroll in trial and trust their kids’ lifes with us, none of this would be possible. So I just wanted to thank everybody else. Thanks for staying awake. It looks like you guys actually did pretty well on questions and answers. I think this is for CME credit. I think there is a link there for educational credit. And again, I want to thank everybody. And this is our home at CS Mott Children’s Hospital, and a very contemporary Fall shot, actually. And just for the record, this is one time when we come here to Phoenix, and Michigan is warmer than Phoenix. Just want to state
that for the record. So, it's a fact. But anyway, thank you. I know it's getting late, but we're happy to answer any questions that you have for me or any other panel member.

ATTENDEE: Kudos on using the gabapentin prospectively to prevent pain in folks.

DR. MODY: Okay, thank you.

MODERATOR: For those of you who didn’t or can’t read the slide, if you look in front of your syllabus, there’s information on how to get your CEUs. It is worth a credit. And thank you, Dr. Mody, so much and your team. How refreshing it is to see a team present. I appreciate the candid conversation about the experience, the trial and error, and what worked. That’s really very informative, and it was good to see the feedback and input from everybody. Thank you very, very much. And thank you all for coming.

[END]