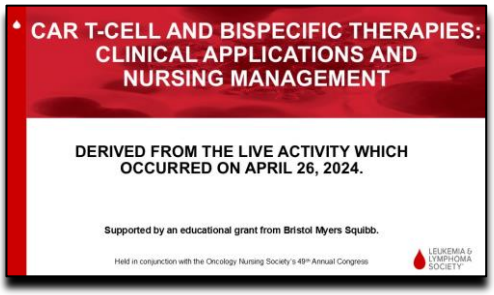
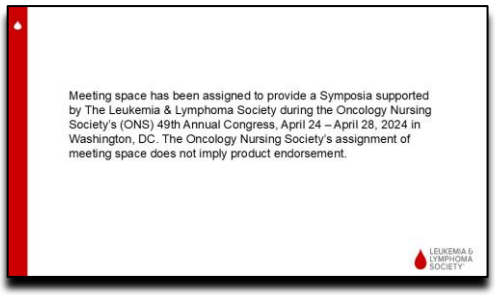


Slide 1: Car T-Cell and Bispecific Therapies: Clinical Applications and Nursing Management

Slide 2: Welcome and Introductions

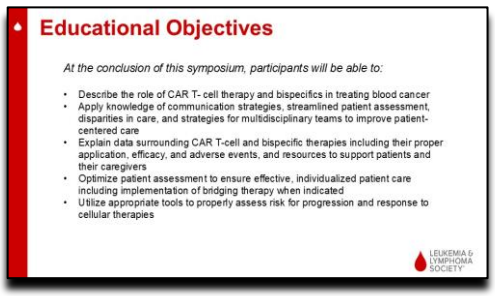
Lauren Berger, MPH: Hello everyone. Thank you so much for being here. On behalf of The Leukemia & Lymphoma Society, thank you for joining us. I hope this symposium provides a fun, interactive, and useful learning experience for all of you.

We will provide an overview of the role of CAR T-cell and bispecific therapies to treat blood cancer, focusing on the nurse's role in caring for patients, including the proper application and managing adverse events. Disparities in care, the importance of the multidisciplinary care team, and resources to support both patients and healthcare professionals will be discussed. Thank you so much to our supporter, Bristol Myers Squibb for an educational grant to support this program today.



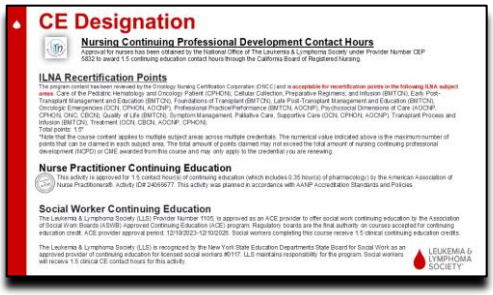
Slide 3: ONS Disclaimer

Meeting space is provided by the ONS and is included on this slide.



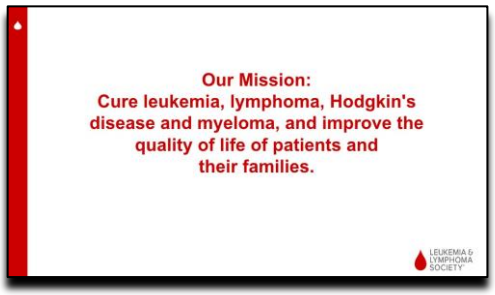
Slide 4: Educational Objectives

The learning objectives for today's program are listed here.



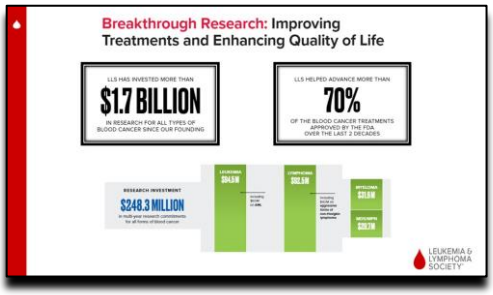
Slide 5: CE Designation

Continuing education information is listed on this slide.



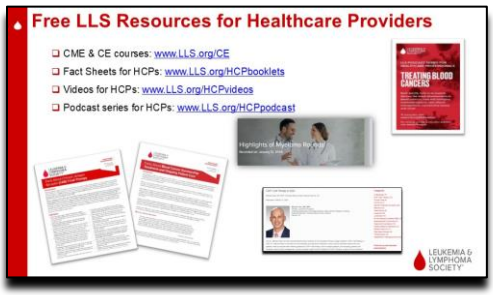
Slide 6: LLS Mission

The mission of The Leukemia & Lymphoma Society is listed on this slide.



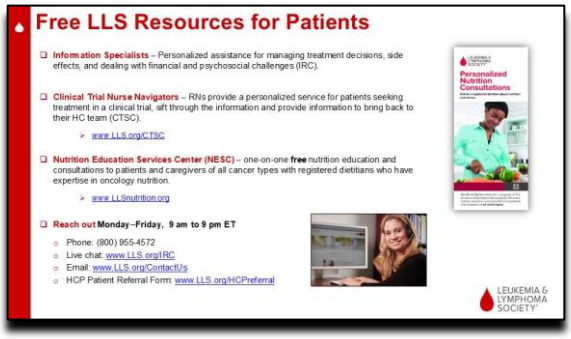
Slide 7: Breakthrough Research

Over the past 70 years, LLS has invested more than $1.7 billion in cutting edge research for all types of blood cancer, funding nearly all of today's most promising advances. LLS supports the full spectrum of research from basic laboratory research to large scale clinical trials, including CAR T-cell therapy early on. The research has great impact for getting and moving therapies to approval and getting them to patients.



Slide 8: Free LLS Resources for Healthcare Providers

I am pleased to share free resources from The Leukemia & Lymphoma Society for both you and your patients. LLS offers CME and CE accredited programs, both online and, obviously, in person here. We have a podcast channel for healthcare providers, and you can listen to those at your leisure in your car or in your office at; various times throughout the month, and we're always adding new and interesting discussions.



Slide 9: Free LLS Resources for Patients

Free resources are available also for your patients from The Leukemia & Lymphoma Society. Information Specialists, which are highly trained oncology social workers and nurses, provide accurate, up-to-date disease and treatment information as well as support resources such as financial. Patients can contact them directly, both at the 800 number you see or online.

Also, you as a healthcare provider, as a nurse, can provide a free referral to The Leukemia & Lymphoma Society for your patients, and we will provide them with the resources and support. Our Clinical Trial Support Center Nurse Navigators are registered nurses and nurse practitioners with expertise in blood cancer. They work one on one with patients via telephone to provide user friendly information and help find clinical trials that are appropriate for that specific patient. They also personally assist them throughout the entire journey, both whether they enroll in a clinical trial or they just need information. They will also provide resources and information for the patient to bring to the healthcare team so that the final decision, obviously, is made with the healthcare team. For information or to refer or connect a patient with an Information Specialist or a Nurse Navigator, please use the URLs listed here; and they're also in your workbook which has copies of all the slides.

To refer your patient for a free one-on-one nutrition consultation with one of our registered dietitians by telephone, this is available for patients of all cancer types, not just blood cancer patients, It's a wonderful opportunity for patients to be able to talk to a registered dietitian.

We also have interpretation services for all of these opportunities for your patients as well as for you. So if their, English is not their primary language, we do have interpretation services.

Slide 10: Free LLS Resources for Patients and Caregivers

LLS also offers blood cancer disease-specific information and support services for patients and caregivers including telephone and Web education programs, videos, and a podcast channel for patients. As you know, we talked about the professional podcast. We have a separate one for

patients. Some of you may know about our financial assistance program, and please keep up to date on our website to find out where money is available for the patients that you are supporting.

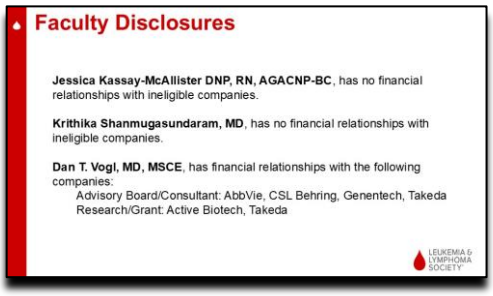
LLS, through culturally and targeted programs and services, we are committed to addressing the needs of both underserved and minoritized patients, both in the community where you live and throughout the country and especially to help those facing systemic and cultural barriers to optimal care.

Slide 11: Free LLS Resources for Patients

On this slide, you see examples of booklets that you can order from LLS at no charge for your patients. They can order them on their own, or you can order multiple copies; and we will mail them to you. We know that you are key to patient treatment and helping them with survivorship challenges. We know that the patients are talking to you, the nurses, in a way that they feel comfortable; and they're there, you're there for them, and we hope that we can be there for you. We are here to support you and your patients, so please reach out to us.

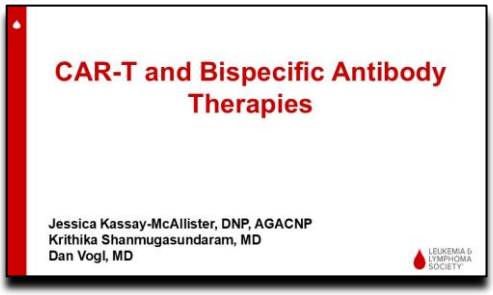
Slide 12: Faculty

I'm now honored to introduce our faculty. Dr. Jessica Kassay-McAllister from University of Virginia, Dr. Krithika Shanmugasundaram, also from University of Virginia; and Dr. Dan Vogl from University of Pennsylvania. Thank you so much for sharing your time and expertise with us today.



Slide 13: Faculty Disclosures

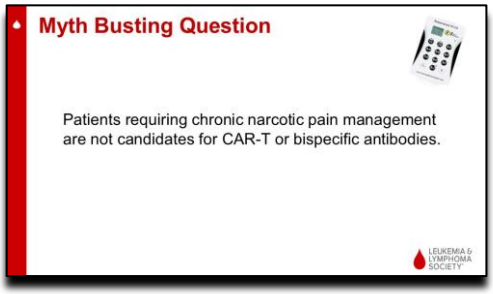
There, the faculty disclosures, as required, are listed on this slide.



Slide 14: CAR-T and Bispecific Antibody Therapies

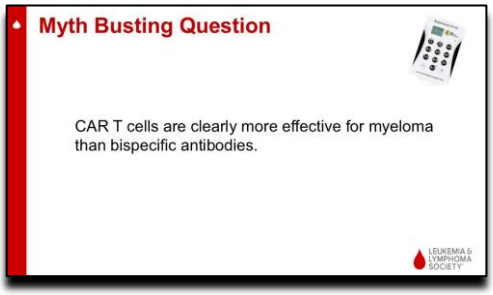
I am now pleased to turn the program over to nurse practitioner, Dr. Jessica Kassay-McAllister and thank you all.

Jessica Kassay-McAllister, DNP, RN, AGACNP-BC: Thank you, Lauren. Good afternoon. I'm Jessica Kassay-McAllister, as Lauren mentioned, and we're going to start off with some myth busters.



Slide 15: Myth Busting Question

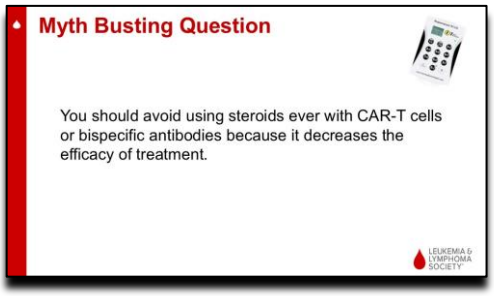
"Patients requiring chronic narcotic pain management are not candidates for CAR T or bispecific antibodies," true or false? 96% of you answered false, and that is correct. So, we actually do consider patients who are on chronic narcotic pain management as candidates for CAR T and bispecific therapy. We do modify their regimen so that they actually can show us whether or not they're having a toxicity or if it's related to the narcotic use.



Slide 16: Myth Busting Question

All right, we're going to go to our next, our next Myth Buster is "CAR T-cells are clearly more effective for myeloma than bispecific antibodies." True or false?

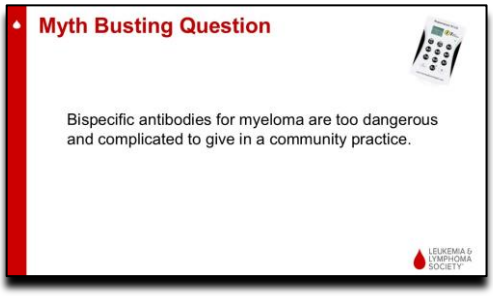
Dr. Vogl: Oaky, so, 68% of you correctly identified that this was false, and the key word here is clearly. Although CAR T-cells are very effective for myeloma, bispecific antibodies are also very effective for myeloma. A lot of us have tried to, generally preferred to go to CAR T-cells for the patients we think are good candidates for them; but the two have not been compared against each other. And we actually don't know in the long run which is going to be the more effective therapies for our patients or whether we'll end up using both.



Slide 17: Myth Busting Question

Jessica Kassay-McAllister: So our third myth buster will be, "You should avoid using steroids ever with CAR T-cells or bispecific antibodies because it decreases the efficacy of treatment." True or false?

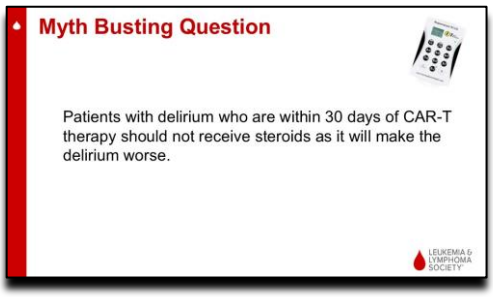
Jessica Kassay-McAllister: That is correct. 85% of you answered this question correctly. We do use steroids in the treatment of this to keep our patients safe because we have neurotoxicities associated with these therapies. Very good.



Slide 18: Myth Busting Question

"Bispecific antibodies for myeloma are too dangerous and complicated to give in a community practice." True or false?

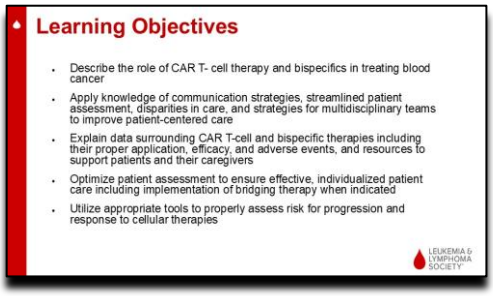
Dr. Vogl: 91% of you answered correctly that that is false. And I'm so glad because as we'll get to later on in the presentation, although some of the early toxicities of bispecific antibodies for myeloma mean that they should be given in a hospital with very experienced personnel in the management of cytokine release syndrome and neurotoxicity, the outpatient dosing given over the long term is actually quite safe and relatively easy to give and one of my main goals in, communicating with my community referring practices is to try to convince them to bring these treatments into the community practice.



Slide 19: Myth Busting Question

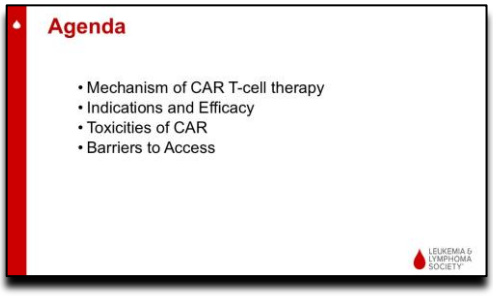
Jessica Kassay-McAllister: And now for our final Myth Buster, "Patients with delirium who are within 30 days of CAR T therapy should not receive steroids as it will make the delirium worse." True or false?

All right, so 83% reported false; and that is correct. Patients who have symptoms of delirium after CAR T-cell therapy may actually be exhibiting signs of neurotoxicity, and so the cornerstone of treatment for that is steroids. There is a risk that it could worsen the delirium, but we should not withhold the steroids for that reason, to ensure safety.



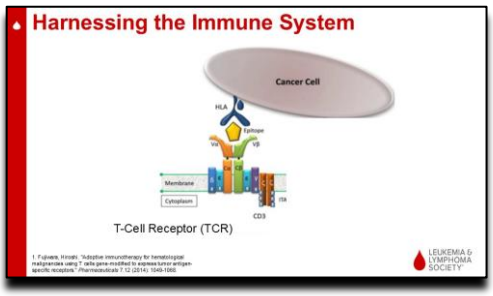
Slide 20: Learning Objectives

Jessica Kassay-McAllister: So, for our learning objectives today, you can see them outlined here.



Slide 21: Agenda

And then our agenda today is to talk about the mechanisms of CAR T-cell therapy and bispecifics, the indications and efficacy, toxicities associated, and barriers to access.

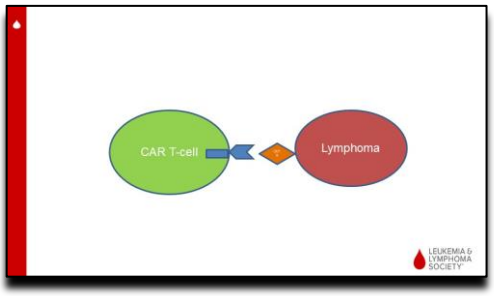


Slide 22: Image

I'm going to turn it over to Dr. Shanmugasundaram.

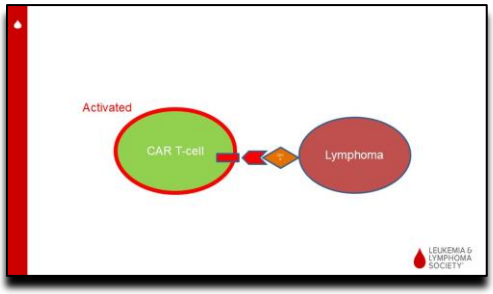
Krithika Shanmugasundaram, MD: Hi, everyone. So, I'll start off by just mentioning that CAR T-cell therapy is a therapy that's really evolved in the last decade or so. So, it's relatively new still to us, but it came about with a promise of allowing us to harness our own immune system to fight cancer.

And so our own T-cells are constantly circulating and monitoring the body for precancerous cells. But in order to identify and destroy them, they really rely on those cancer cells to exhibit an antigen that looks foreign to them. And so this is often why the cancer cells go undetected and escape and grow. CAR T-cells, however, allow for a mechanism where we're able to identify those cancer cells without them needing to kind of say, "Hey, I'm cancer, and I'm here." And so that's been really potent in being able to fight them.



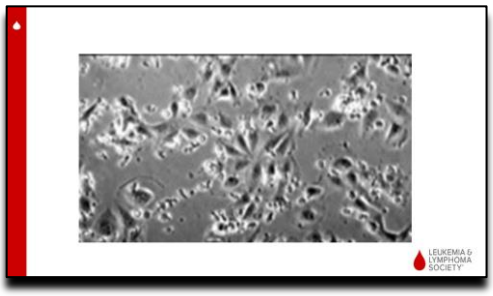
Slide 23: Image

So this is a schematic of how CAR T-cells work. So, when you have a cancer cell that's expressing an antigen like CD19



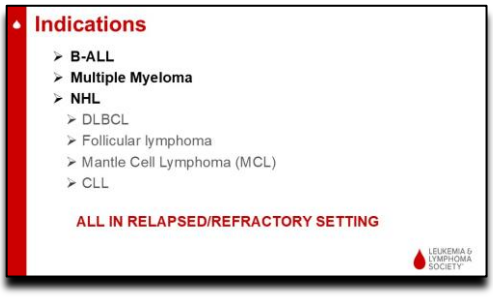
Slide 24: Image

the CAR T-cell is able to recognize it, hang onto it. It gets activated, and then that cancer cell gets destroyed.



Slide 25: Image

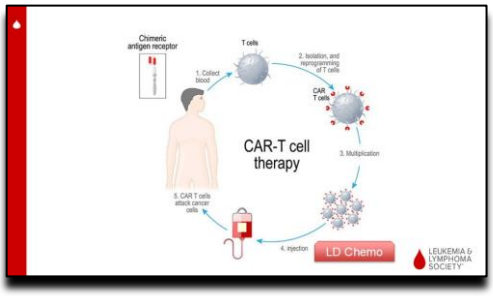
This is just a video under the microscope of how CAR Ts, CAR T-cells in action.



Slide 26: Indications

Currently we have several indications where CAR T-cell therapy is used to treat our patients; and they're listed here. So, B-cell ALL, multiple myeloma, and non-Hodgkin's lymphoma with multiple subtypes now have CAR T-cell therapy approved.

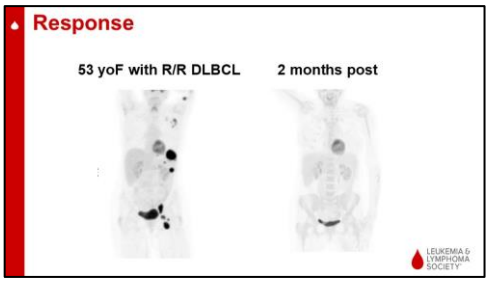
However, it's important to note that these CAR T-cells are really used in the relapsed or refractory setting and not necessarily first line.



Slide 27: CAR-T cell therapy

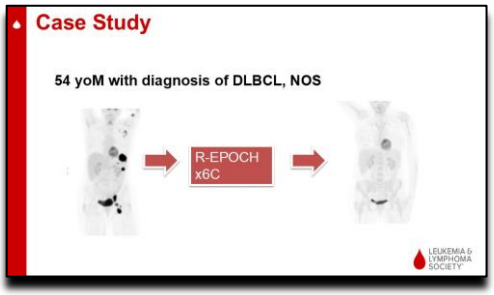
Jessica Kassay-McAllister: So, this is a little schema about CAR T-cells and how we actually collect the T-cells. So, we have our donor. We collect our T-cells. They're shipped off to the manufacturer where they are engineered, and then they are brought back. And once they return to the facility, we start a chemotherapy called lymphodepletion. It's a three-day chemotherapy, and this is not actually the treatment, but this allows us some immunologic space to receive those T-cells so that they can have the expansion. And it also has the cancer cells present the antigen at the surface so the T-cells easily recognize the tumor cells.

And then usually on day 4 or day 5, just depending on your facility, we then infuse the T-cells. And this is not, you know, the height of the time, right, so Day 1 when you're receiving your cells is really not an exciting day. Yes, you're getting your cells, but in the days to come is when we really see those toxicities.



Slide 28: Response

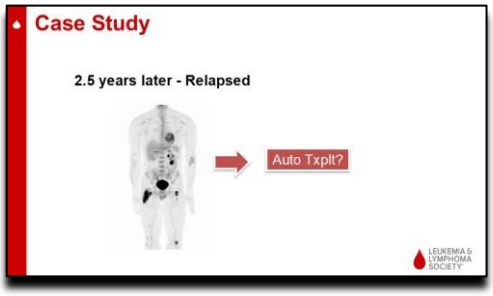
Dr. Shanmugasundaram: So, this is an example of one of our patients who received CAR T-cell therapy when her diffuse large B-cell lymphoma had relapsed. And you can see on the left the areas of disease. And just two months after she received a CAR T-cell therapy, she got a complete response.



Slide 29: Case Study

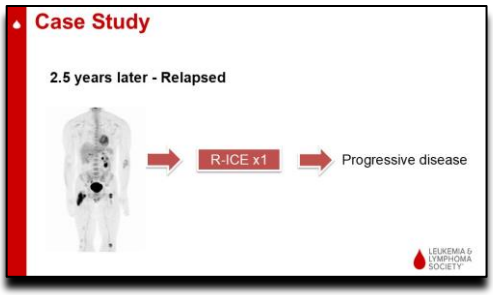
So, in order to kind of figure out where CAR T-cell therapy fits for, in the line of treatments for our patients, I thought maybe we could go through a case.

So, this is a case of a 54-year-old gentleman with diagnosis of DLBCL, comes to see you in clinic. And we decide to start him on first-line chemoimmunotherapy with chemotherapy and rituximab.



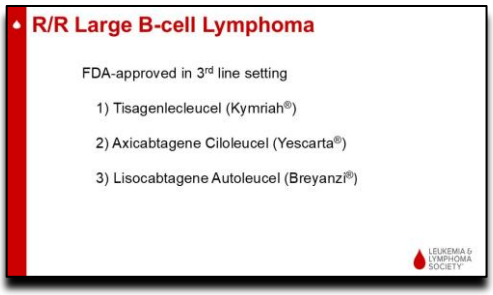
Slide 30: Case Study

He does go into a complete remission, however, sees you back in clinic 2-1/5 years later and has evidence of relapsed disease of his lymphoma. Usually in this case, we would consider this patient for an autologous transplant. That's been the standard of care for many years. And in order to get to an autologous transplant, you have to give them salvage chemotherapy, so more chemo.



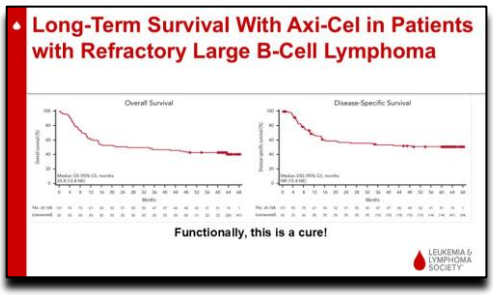
Slide 31: Case Study

And so we went ahead and gave him a cycle of R-ICE. However, after that, his disease progressed; and he didn't actually achieve the remission in order for us to take him to an autologous transplant.



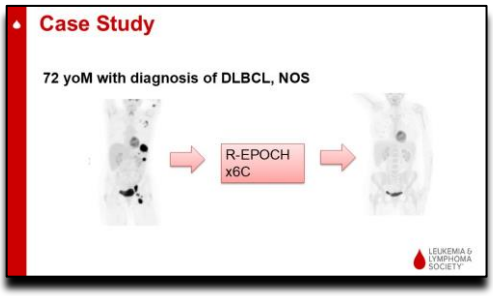
Slide 32: R/R Large B-cell Lymphoma

And now we have a way to still treat his disease that has kind of blown through this second line of chemo with CAR T-cell therapy, and we have three products that have been FDA approved in this setting. And you can see them here – tisa-cel, axi-cel, and liso-cel for short.



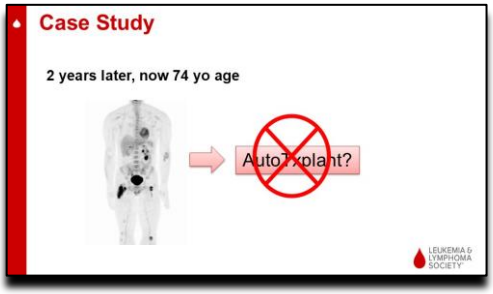
Slide 33: Long-Term Survival With Axi-Cel in Patients with Refractory Large B-Cell Lymphoma

And now we have long-term data from axi-cel at the five-year mark that was recently published. And you can see on these curves, what we see is that if those patients have achieved a CR and remain in CR at the 12-month mark, that's what you see at the bottom, they remain in that CR for about five years. And so really we're considering CAR T-cell therapy as functionally a cure for our patients.



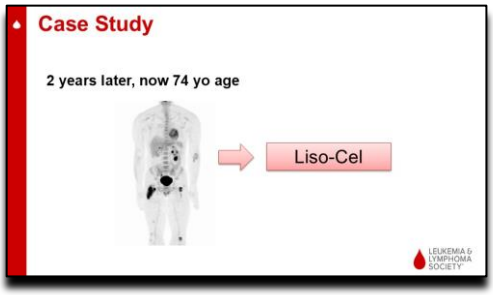
Slide 34: Case Study

I wanted to go through another case, just to illustrate where CAR T-cell can fit into our treatment schema. So, in this case we have an older gentleman, a 72-year-old gentleman with a diagnosis of large cell lymphoma. He also gets chemoimmunotherapy as first line and end up having a CR. Now two years later, he's also older, 74, and comes back with relapse. In the interim, he's, unfortunately, suffered an MI; and you're trying to figure out what's the next line of therapy.



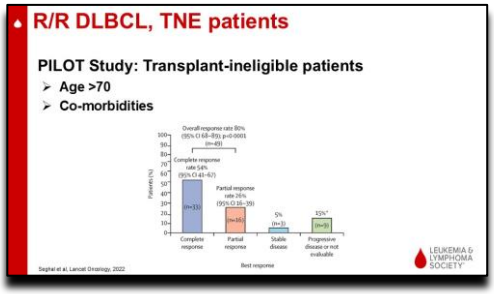
Slide 35: Case Study

Unfortunately, this patient doesn't really qualify for an autologous transplant because of his comorbidities and his age.



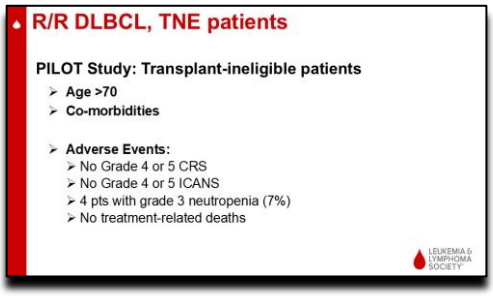
Slide 36: Case Study

And so we've got to figure out what else we can do. Recently, CAR T-cell therapy has been approved in this setting for patients who are transplant-ineligible in the second line, specifically with liso-cel as the product.



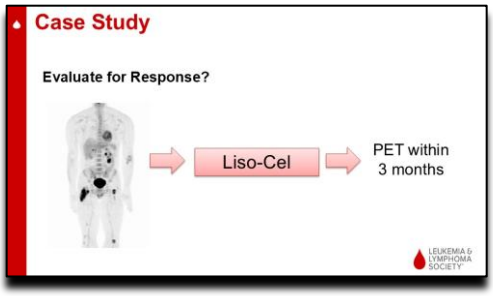
Slide 37: R/R DLBCL, TNE patients

And that was based off of this study, the PILOT study, which included patients who were transplant-ineligible based on their age or comorbidities. And you can see that these patients did see a CR rate of 54%, which is pretty significant.



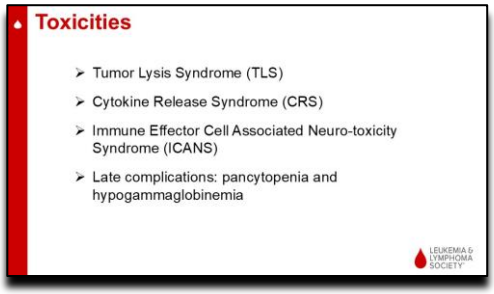
Slide 38: R/R DLBCL, TNE patients

And we're very interested in the toxicity profile for our patients who can't go, undergo transplant because that's really why they can't undergo transplant is because it's too toxic for them. But we were pretty reassured because the data really shows that CAR T-cell therapy is pretty well tolerated with not a lot of severe adverse events.



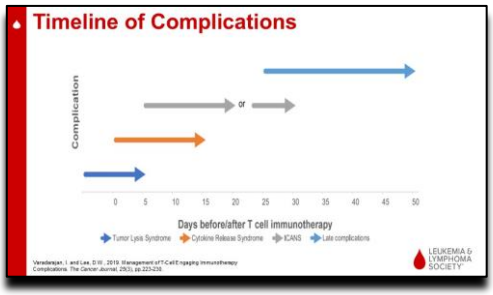
Slide 39: Case Study

So once our patients receive CAR T-cell therapy, how do we evaluate for response and make sure that it is working? So, after they get the CAR T-cell therapy, standardly we will get a PET scan at the three-month mark to evaluate for response; and that's really how they were evaluated on the trials. In our practice, we do tend to get a PET scan a little bit earlier, probably around the six- to eight-week mark just to make sure that we're on the right track and making sure that we don't need to switch to another therapy in case they're progressing.



Slide 40: Toxicities

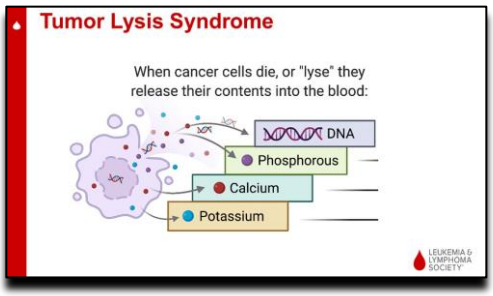
Jessica Kassay-McAllister: So, now we're going to talk about some of the toxicities. The first one during the lymphodepletion, we are concerned with tumor lysis syndrome. I'm sure most of you are very familiar with that. Cytokine release syndrome after the CAR is given. Immune effector cell-associated neurotoxicity syndrome, further known as ICANS. And then our later complications such as pancytopenia.



Slide 41: Timeline of Complications

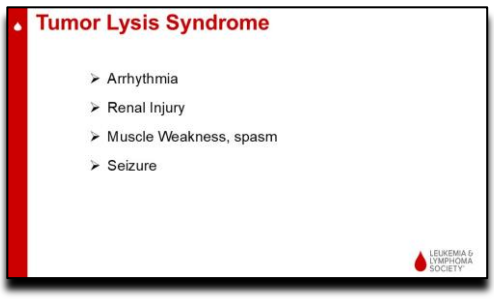
So, this is a nice visual to show you the timeline of when these things should occur. As you can see, the blue line or the first blue line, the darker one, tumor lysis syndrome can happen from day 1 of lymphodepletion up to day 5. Right, so even into the CAR T, after your CAR T infusion, so you want to monitor for that as well. Then you have cytokine release syndrome that can start from day 0 or day 1, the day that they receive their infusion, up until day 15. Sometimes we've seen it a little bit further out.

And then we have ICANs, which can start roughly around day 5 to day 20, and then you can see more later ICANS which is known as delayed ICANS, 25 to day 30. And then our later complications as indicated on the slide.



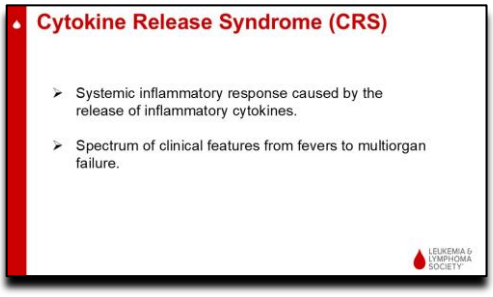
Slide 42: Tumor Lysis Syndrome

Dr. Shanmugasundaram: So just a quick refresher on tumor lysis syndrome, so this, as Jess mentioned, if it occurs, will occur because of the LD chemo that they're getting, which can decrease their tumor burden a little bit before you go into CAR T-cell therapy and gives you that immunologic space, as she mentioned.But as those cancer cells die, they do release all their contents into the bloodstream.



Slide 43: Tumor Lysis Syndrome

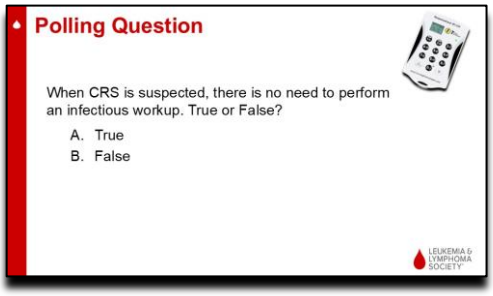
And because it's such an enormous amount, it can cause problems due to these electrolytes accumulating. And specifically, these electrolytes can cause arrhythmia. They can promote precipitation of uric acid stones and cause renal injury, muscle weakness, and spasm from the calcium abnormalities and then sometimes even as severe as a seizure.



Slide 44: Cytokine Release Syndrome (CRS)

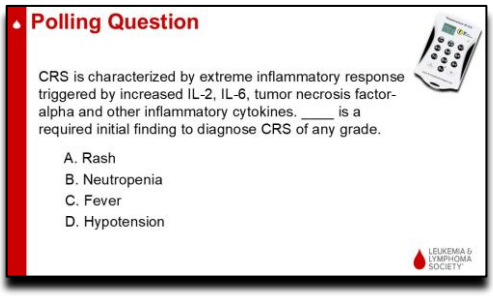
Jessica Kassay-McAllister: So, talking about cytokine release syndrome, this is a systemic inflammatory response caused by the release of inflammatory cytokines. And you can have a spectrum of clinical features from fevers to multiorgan failure. Oftentimes, it can present itself very similarly to sepsis. So, this is something that we talk about frequently in our setting is that we want to make sure that we're also conducting a neutropenic workup at the same time as treating the CRS. So, it's very, very important that we're doing those two things in tandem.

As you remember during the days of COVID when our patients were first presenting, they were presenting septic; and they had a lot of cytokine release. And we were giving them an IL-6 blocker known as tocilizumab. So, it's the same idea here. We give toci in the same setting.



Slide 45 Polling Question

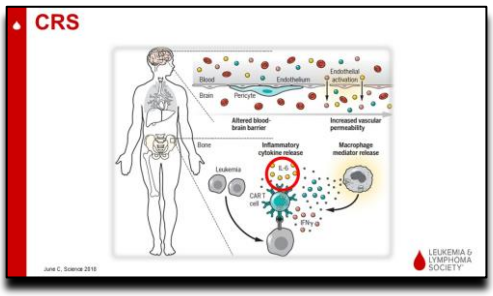
When CRS is suspected, there is no need to perform an infectious workup." True or false? Excellent. 97% of you said false, and that is correct. As I just mentioned, you want to make sure that you're doing that infectious workup in tandem with treating CRS.



Slide 46: Polling Question

Dr. Shanmugasundaram: All right, our next polling question. "CRS is characterized by extreme inflammatory response triggered by increased IL-2, IL-6, and tumor necrosis factor alpha, and other inflammatory cytokines. "Blank" is a required initial finding to diagnose CRS of any grade." Is it rash, neutropenia, fever, or hypotension?

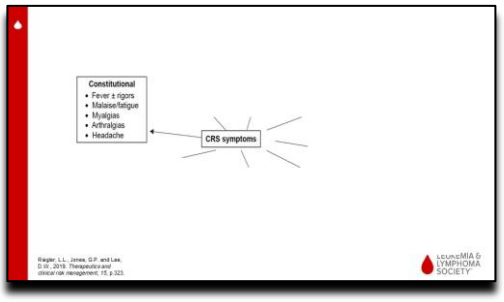
All right, so 81% said fever, and you are correct. So while all four of these can happen during CRS, fever is the hallmark of CRS.



Slide 47: CRS

Dr. Shanmugasundaram: So this schematic is really just a visual representation of what happens in CRS within the body. So, as we mentioned, it's the release of inflammatory cytokines; and that happens because of the CAR T-cells interacting with the tumor cells as well as some of the B-cells, and it leads to this massive release of cytokines.

But one of the major players is IL-6, and that's why that is one of the targets in the therapy that we use, the tocilizumab. You can see that here.

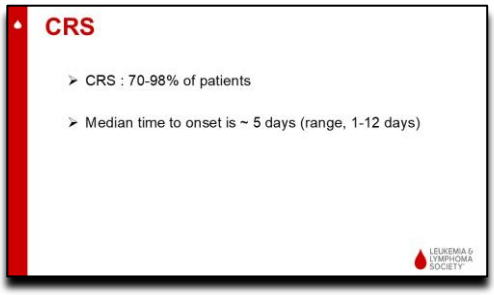


Slide 48: Image

So, as I mentioned, fever is the hallmark of CRS, so everyone who has CRS will have a fever. So, it's important to recognize fever initially and then work it up appropriately. However, CRS can affect almost any organ system in the body and can present in many different ways, such as tachycardia. It can affect the GI system, the skin, like we mentioned a rash. Hepatic dysfunction, renal dysfunction, and respiratory dysfunction. The respiratory dysfunction is also important to note because that can indicate that we need to escalate therapy.

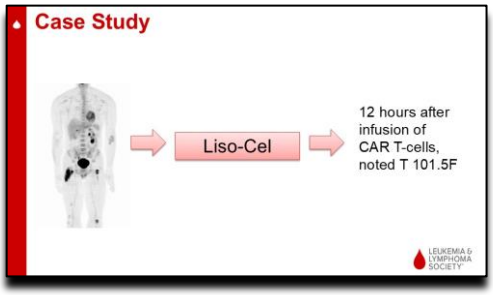
Jessica Kassay-McAllister: And I think this is an important factor as well, respiratory. This is an area of growth in our area. This is caused by capillary leak syndrome, and you can have pulmonary edema, and I think it can be very scary in the outpatient setting in the infusion center. So, making sure that you recognize this immediately so that you can do appropriate intervention.

Dr. Shanmugasundaram: And then in really severe CRS, you can also see irregularities with the coagulation cascade; and so it's important to recognize and evaluate for that as well so that we can give appropriate supportive care in that setting.



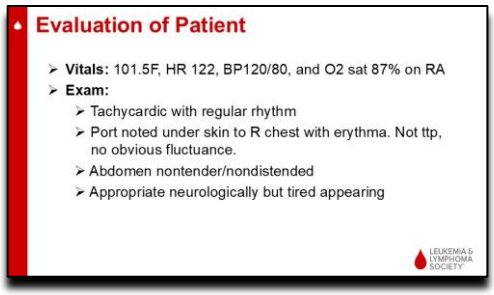
Slide 49: CRS

So, CRS occurs in about 70 to 98% of patients who receive CAR T, and that's really dependent on the product. So, certain products I will counsel my patients and say you will have some level of CRS, you will have a fever. And as Jess had mentioned earlier, the median time to onset is usually around the five-day mark, but it can happen as early as day 0. So, very common and something that we have to pay attention to.



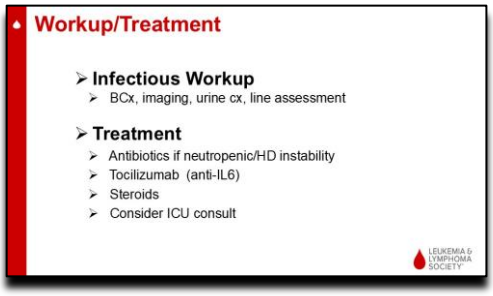
Slide 50: Case Study

All right, so let's go back to our patient. So, they received the liso-cel CAR T-cell therapy. Infusion went well. However, about 12 hours after the infusion, it's noted that they have a temperature of 101.5.



Slide 51: Evaluation of Patient

All right, so we're going to go ahead and evaluate our patient, get a set of vitals. We notice that, yes, they are febrile, and they're tachycardic. Blood pressure's okay, but now they have a new oxygen requirement. Setting to 87% on room air. Otherwise, the exam, again, confirms the tachycardia. The port does have some erythema but no obvious fluctuance. Abdomen's okay, and neurologically they seem appropriate; but they are a little fatigued.



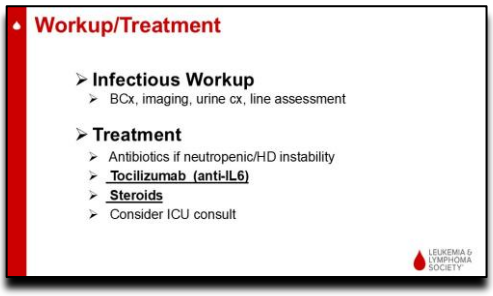
Slide 52: Workup/Treatment

All right, so what should we do next for workup? First and foremost, you know, go back to the basics. We want to do an infectious workup for someone who has a fever. So that can include blood cultures, imaging, urine, and a line assessment.

And then how do we go forward with treatment? So again, if you're thinking infection, you want to give antibiotics, especially if they're neutropenic. And then make sure that they are hemodynamically stable. If not, we need to address that with fluids and resuscitation.

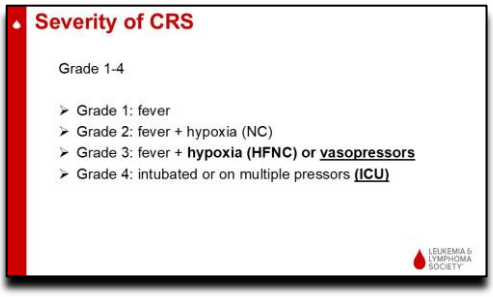
Next, we talked about tocilizumab, so that's an anti-IL-6. So, if you're consider, concerned about CRS, it's absolutely fine to go ahead and give some tocilizumab, especially in this case where you're having other organs affected such as the respiratory system; and steroids are also important.

We don't always give steroids for every case of CRS; but when it involves hypoxia, that's when we start pulling the trigger on that because toci alone is not going to help our patient there. And then it's never wrong to phone a friend, so we often do consider an ICU consult in our patients that are just not getting better with treatment.



Slide 53: Workup/Treatment

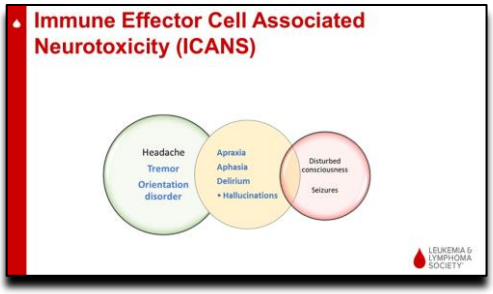
So of these treatments, I just wanted to point out that the toci and the steroids are kind of the CRS-directed treatments. But we need to make sure that we provide amble supportive care and consider the other things on our differential.



Slide 54: Severity of CRS

We hinted a little bit towards the severity of CRS and how to look at that. So, it's graded 1 through 4. Grade 1 is a fever and, like I said, most people will have that. Grade 2, however, is fever and now hypoxia, so it's really, that's part of why it's so important to evaluate the respiratory status in our patients. Grade 3 is when you start thinking about, oh, their care is escalating. We probably need an ICU consult. They're going to need more than what we can do on the floor and that includes high flow nasal canula or the addition of vasopressors. And then Grade 4 is when they're absolutely in the ICU and

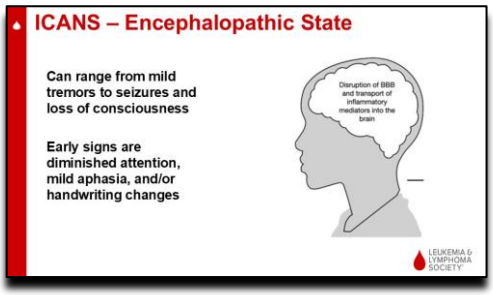
they're intubated and need, and multiple pressors are needing ventilation support.



Slide 55: Immune Effector Cell Associated Neurotoxicity (ICANS)

Jessica Kassay-McAllister:

So this is a quick visual. We're going to move into immune effector cell-associated neurotoxicity, ICANS. And this just gives some of the symptoms that you can see in different grading spectrums – headache, tremor, orientation disorder, apraxia, aphasia, delirium, hallucinations. These are pretty easy to identify. Some of these symptoms we rely on our patients to let us know about or their caregivers, especially when we're treating the patients in the outpatient setting. And then disturbed consciousness and seizures, again, would be a Grade 4; and they would require an ICU stay.

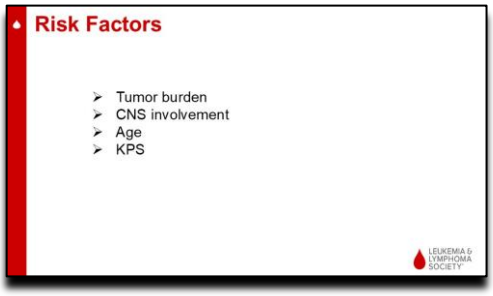


Slide 56: ICANS – Encephalopathic State

Dr. Shanmugasundaram: So, ICANS, again, is kind of this encephalopathic state; and as Jess mentioned, the symptomology can have a wide range from just mild tremors to severe seizures and loss of consciousness.

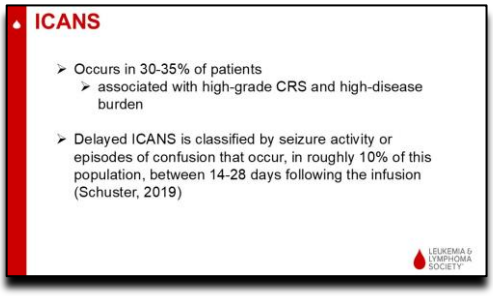
We think that ICANS is related to the inflammation that's caused by the CAR T-cells interacting with the tumor cells. But I have to say we don't exactly know what all goes into that pathophysiology. But we believe that that inflammation does cause this disruption of the blood-brain barrier, and sometimes we can see that even with the healthy fluid that we'll pull and send off for those specialized studies.

It's important to pay attention to early signs of ICANS, and that can just be kind of diminished attention. Something is a little bit different when, then when you first admitted the patient. Mild aphasia, and I will say I think aphasia's probably one of the most common symptoms in ICANS, and so that's something to definitely pay attention to. And, it can be as subtle as handwriting changes. And so we often do get a handwriting sample at baseline when they're admitted and make sure that we evaluate that every time we're evaluating for ICANS in our patients.



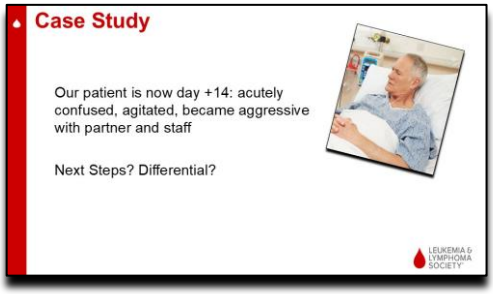
Slide 57: Risk Factors

Jessica Kassay-McAllister: So, as Dr. Shanmugasundaram mentioned, we get a handwriting sample prior to doing the CAR T therapy, right? So, we'll talk about risk factors first; and then we'll go. So, risk factors for ICANS is tumor burden, CNS involvement, age, and KPS. Tumor burden, the larger the tumor burden, the higher the risk. CNS involvement, obviously, that tells you right there they have CNS involvement. They're going to likely have ICANS. What we do for our patient population is we refer them to neuro-oncology, and we get a risk assessment prior to CAR T therapy. And this is based on the number of different things, these four listed here, as well as our assessment, and we come together as a team.



Slide 58: ICANS

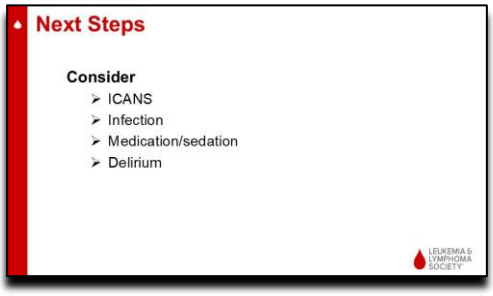
So, ICANS occurs in 30 to 35% of patients. It's associated with high-grade CRS and high disease burden, as I mentioned. And then delayed ICANS. I know I mentioned this earlier is classified by seizure activity or episodes of confusion that occur in roughly 10% of this population later on, 14-28 days, but could be a little bit outside of the 28 days as well.



Slide 59: Case Study

Dr. Shanmugasundaram: All right, so we're back to our patient. He is now day 14 after getting his CAR T-cells infused. You have successfully treated his CRS, and he's been doing okay for the last couple of days.

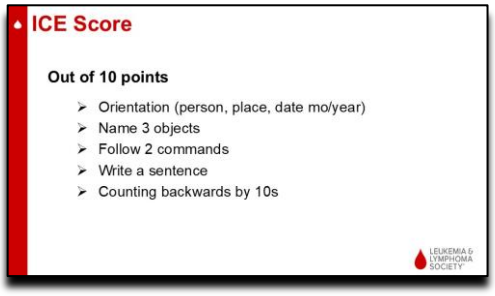
However, now you're evaluating him on day 14. He's acutely confused, agitated, and you've noticed that he became aggressive with the staff, and there's also reports that he was aggressive with his partner.



Slide 60: Next Steps

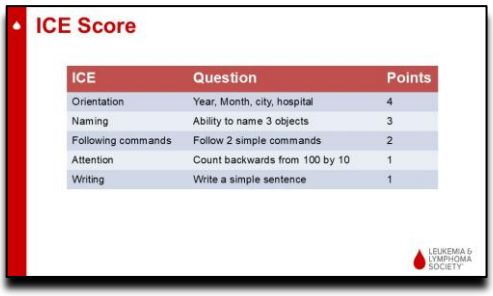
So, what are your next steps; and what are you thinking is going on that has caused this change? So, absolutely, we should consider ICANS in our patient who just received CAR T-cell therapy, is still well within the window of having neurotoxicity from it.

But we have to make sure that we consider other things as well, so always consider infection, especially CNS infection. But really any type of sepsis can cause changes in mental status. Doing a thorough medication review because that can also lead to changes in mental status. And then in-hospital delirium can certainly contribute to these changes as well.



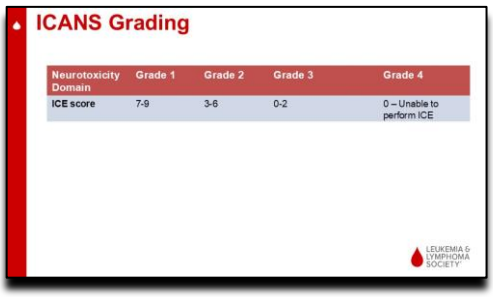
Slide 61: ICE Score

Jessica Kassay-McAllister: So now we're going to talk about the ICE scoring. This is a tool that we utilize to kind of identify ICANS in our patients. The first is orientation, as we do for all of our patients – person, place, date, month, and year. We have them name three objects, and we have them recall those three objects later in our interview process. Have them follow two commands at the minimum. That sentence, we're coming back to that. The sentence that we got at baseline, we continue to monitor that every time we get an ICE score. And then we have them count backwards by ten, starting at 100.



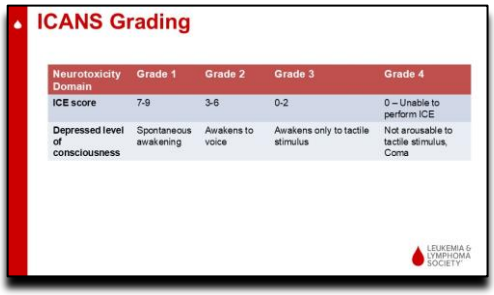
Slide 62: ICE Score

I know it sounds very simple to count backwards by ten, but when they have ICANS, it is not.
So, this is our ICE score. This is what the tool looks like. In EPIC, it looks very similar.



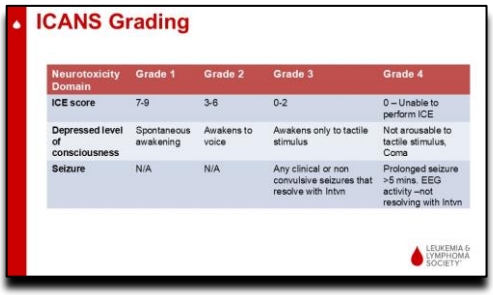
Slide 63: ICANS Grading

Dr. Shanmugasundaram: So then ICANS grading, I would say this is a little bit harder, for me at least, to commit to memory, so I always look it up.
But, you can see the components that go into it, and ICE score is one of them.



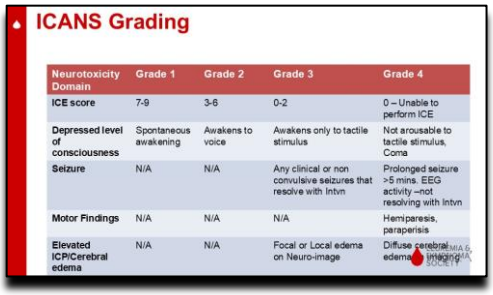
Slide 64: ICANS Grading

But we also look at their level of consciousness, whether or not they have seizure activity,



Slide 65: ICANS Grading

And so oftentimes our patients will be put on a continuous EEG to confirm this.



Slide 66: ICANS Grading

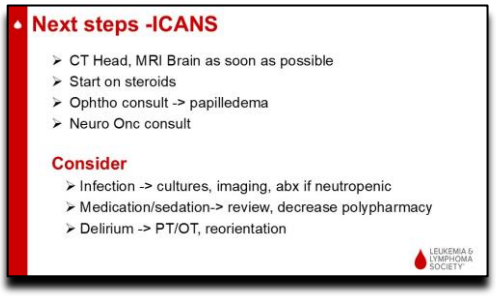
And once they have a seizure, you can see they're automatically at a Grade 3. And then motor findings and evidence of cerebral edema also puts them at that higher grade of Grade 3, and so we, this is where our neuro-oncology consult really comes in handy. And so anyone who we're concerned about having ICANS in the hospital, we'll ask neuro-onc to come by, they'll help us with the EEG. A lot of times they'll recommend an LP with an opening pressure that can help with evaluating for cerebral edema. And then we also ask for an ophthalmology consult to look for papilledema, and again, that can also help us understand if they have cerebral edema.

Slide 67: Cartox App

Jessica Kassay-McAllister: So, this is a tool that we utilize at our institution. It's called the Cartox mobile app. It's available on iPhone and Android, and it was developed by an APP at MD Anderson. And this is maintained and kept up to date with the most up-to-date ASTCT consensus grading. So, MD Anderson manages this. It's free for use, and everybody can use it. It's very nice to use.

So what you can do is put your grading in, and once you hit your grade, if you can see the third sample there, it will populate the grade; and then once you hit Grade, it will show

you the cascade of next steps. What exactly you should do. It identifies how you should treat CRS and, of course, your neutropenic workup. And so it's a great tool to use.



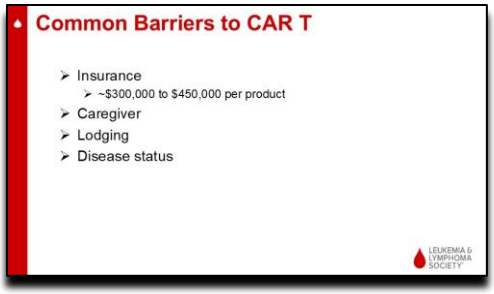
Slide 68: Next Steps- ICANS

Dr. Shanmugasundaram: So back to our patient who we think potentially has ICANS. What do we do next?

So, we want to evaluate for all of those aspects of grading that ICANS; and so part of that could be looking at a CT head or a MRI brain to evaluate for cerebral edema but also potentially other etiologies that could be contributing to what's going on. And then the cornerstone of treatment, once you suspect ICANS in this setting, is to start on steroids.

So, this is an important distinction between ICANS and CRS, so at this point we no longer can kind of wait and use things like toci or Tylenol. Those are really not effective in ICANS, so you've got to start with steroids. And then I mentioned we asked our ophtho colleagues to come help us out and our neuro colleagues as well.

And then, remember, we also, in the back of our minds, also think about all these other things that could be causing this change in mental status, so suspecting infection, do all the things for infection, right, cultures, imaging, antibiotics. Medication list review is often really helpful to get rid of the things that we don't need that could be causing changes in mental status and then delirium, you know, frequently just reminding everyone who's involved in the patient's care to help with reorientation; and I think PT and OT kind of often help a lot in this situation as well.

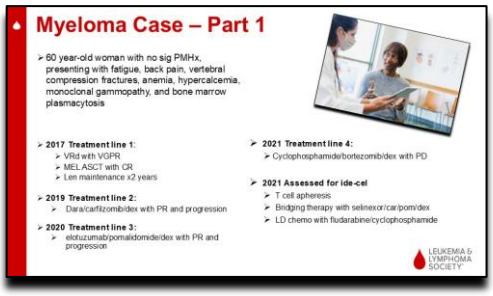


Slide 69: Common Barriers to CAR- T

So, you know, while CAR T-cell therapy has been a really big advancement in our field in the last decade, there are, unfortunately, some barriers that our patients commonly face in receiving this therapy, the first one being insurance. So, when a patient presents for evaluation of CAR T-cell therapy, we cannot even consider giving it to them unless they have insurance because this therapy is so expensive, ranging from 300 to $450,000 per product. And so this is an unfortunate reality that a lot of our patients face, and we will often be able to help at least expedite getting insurance, but that is a huge barrier.

Caregiver availability. This is also another barrier that our patients face, and not everyone has a caregiver that's readily available to be able to be there 24/7 for the several weeks that we need them on hand to evaluate for things like mental status changes or fevers and be able to alert us or bring the patient in for evaluation when that happens. Lodging, we do ask our patients to stay nearby for at least six to eight weeks after discharge. And so luckily the companies can often provide lodging for a good portion of that time, and then we're able to help find some resources for our patients who need lodging for longer.

And then disease status, another thing that is difficult to address and sometimes, unfortunately, out of our control. So, when patients' disease is unable to get under the control that we need in order to proceed with CAR T-cell therapy or it's just growing too fast for CAR T-cell therapy to be safe, that often prevents us from being able to provide that for them.



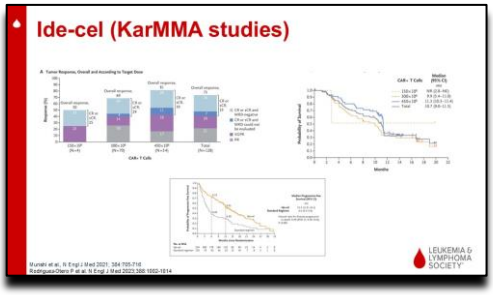
Slide 70: Myeloma Case – Part 1

Dr. Vogl: So my colleagues here specialize much more in lymphoma, and CAR T-cells were initially approved primarily for B-cell malignancies, lymphoma, and ALL. And myeloma has been a little farther behind, but as of three years ago now, we had our first CAR T-cells approved for myeloma as well and, right now, primarily in later line therapies. And so I'm going to take you through a case and talk about not just CAR T-cells for myeloma but also one of the other ways we have of redirecting T-cells to attack cancer which is bispecific antibodies.

So this patient, a 60-year-old woman who initially presented with fatigue, back pain, vertebral compression fractures, anemia, hypercalcemia, and bone marrow plasma cells got initial therapy; and this is what standard of care therapy looked like a few years ago with VRd with a really good response, a melphalan autologous stem cell transplant with a complete response, and two years of lenalidomide maintenance, but then relapsed and got a daratumumab-carfilzomib combination with a nice response but then progression. Then an elotuzumab-pomalidomide combination with a response in progression in fourth-line therapy then with a cyclophosphamide-bortezomib combination.

And so by now has utilized all of the most effective therapies that we had for mult-, multiple myeloma and a few years ago was assessed; and at the time, in 2021, the product that we had was idecabtagene vicleucel or ida-cel, also known by its brand name, Abecma, and underwent in the same exact way that we, you just heard about for lymphoma a T-cell apheresis, some bridging therapy, which is often something that we

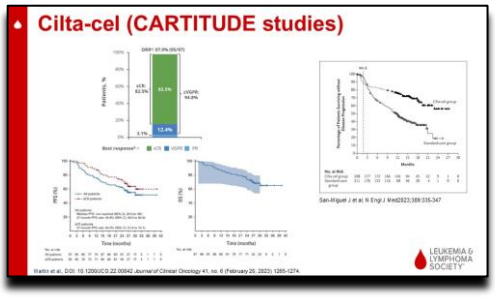
have to do in multiple myeloma to get the disease under control to make it safer to go through the CAR T-cell therapy, so in this case you can see a complicated four-drug regimen, including the XPO1 inhibitor selinexor. Then the same kind of lymphodepleting chemotherapy, also with fludarabine and cyclophosphamide.



Slide 71: Ide-cel (KarMMA studies)

Just like is generally done with lymphoma and then received ida-cel. And up until three weeks ago, this is exactly how we've been using CAR T-cells in myeloma, based on clinical trials that showed a high response rate on the left and some long responses in patients with very relapsed refractory multiple myeloma. And the initial approval for our CAR T-cells was based on these single-arm trials showing good response rates and long responses in people with very refractory disease.

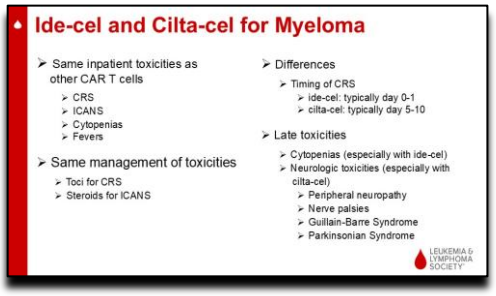
Just recently, we had data earlier in the course of disease. So for ida-cel, this was a trial looking at patients with at least two prior lines of therapy showing improved progression-free survival compared to a, some other standard of care treatment regimen. And for ida-cel, the median progression-free survival in this setting was just over a year, 13 months. Which was significantly better than what was seen with standard chemotherapy treatments.



Slide 72: Cilta-cel (CARTITUDE studies)

The other treatment, the other CAR T-cell that we have, ciltacabtagene autoleucel, or cilta-cel, also known as Carvykti, was also approved about a year after ida-cel based on the left side there, a very high response rate. Almost 100% of patients had responses. And long progression-free survival and even pretty good overall survival in patients who had been through at least four prior therapies for multiple myeloma.

And then similarly, just recently, we had data come out from a trial comparing cilta-cel to standard-of-care therapies in patients much earlier in their disease with just one to three prior lines of therapy for their multiple myeloma. And as you can see on the right, progression-free survival was substantially better. And really looked particularly good with a median progression-free survival that's exceeding two years and was just recently defined as closer to three years. So the results with cilta-cel looked particularly good.



Slide 73: Ide-cel and Cilta-cel for Myeloma

These two products are very similar to the CAR T-cells that we were just talking about for lymphoma. So, we see the same inpatient toxicities as other CAR T-cells with cytokine release syndrome and ICANS being the primary problem that patients go through. We see the same kind of cytopenias from the lymphodepleting chemotherapy and the same problems with assessing fevers and trying to decide whether they are from cytokine release syndrome or from infections.

And we have the same general management approach to those toxicities so that the cornerstone of treatment for cytokine release syndrome is tocilizumab; and really part of our success in getting patients through this is early recognition of cytokine release syndrome and early application of tocilizumab.

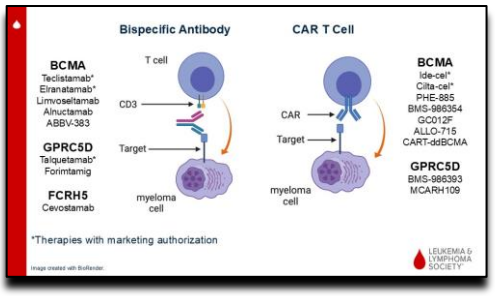
We used to be kind of afraid that somehow tamping down the cytokine release syndrome would impair the efficacy of the CAR T-cells, and I think we now have zero concern about that so that if somebody's having cytokine release syndrome, if it's severe enough that they need tocilizumab, we try to get that to them as quickly as possible. And the same thing with steroid therapy for the neurotoxicity for ICANS. Once somebody has neurotoxicity, we want to treat them with steroids as soon as possible; and we really don't worry about the possibility that the steroids will have an adverse effect on the CAR T-cells. In fact, if anything, we've learned the opposite, that these CAR T-cells, once they start expanding in a patient, it's really hard to stop them, even if you throw a lot of steroids at them. And so we're much more worried about the toxicity end on the management than we are on the impairing the CAR T-cells.

So, what are some of the differences? Really, not a whole lot, but we do see some differences in the timing of the cytokine release syndrome. And actually specifically in myeloma, we've noticed a big difference between our two products so that with ida-cel, the kinetics of the cells' expansion, the dose that we give mean that the cytokine release syndrome typically comes really early – often on the day that we give the CAR T-cells or, if not, then the day after. There's kind of a tail over the following five to seven days where you can see cytokine release syndrome. But usually it's very early.

Whereas with cilta-cel, typically it occurs five to ten days after giving the CAR T-cells. And so this means that when we admit our patients and give them cilta-cel, they have five incredibly boring days in the hospital where absolutely nothing happens. You just have to remind them that it's still probably coming because the risk of cytokine release syndrome, especially with cilta-cel, is close to 100%.

And then we also see late toxicities, not so much late ICANS. In fact, I don't know if I ever remember seeing that in a patient with myeloma getting CAR T-cells. But cytopenias, which can sometimes last even two to three months after CAR T-cells, and I think we especially see that with ida-cel. And then late neurologic toxicities, which we've especially seen with cilta-cel, which can include peripheral neuropathies and cranial nerve palsies. Those usually get better with management, include mostly steroids. And then two devastating complications, Guillain-Barré syndrome and a syndrome that looks like Parkinson's disease with slowed movement and slowed thinking. And those can be really tough and often don't clearly get better. Luckily, the risk of these late neurologic toxicities is low.

And one of the things that we've learned in giving CAR T-cells for myeloma is that the late neurotoxicities and the especially severe cytokine release syndrome and ICANS are seen primarily when we give them to, CAR T-cells to patients whose myeloma is actively progressing out of control at the time that the CAR T-cells go in. It's a combination of disease burden and the pace of progression. And when both of those are high, the risk of severe complications are much higher. So a lot of what we've learned to do is give bridging therapy between collecting the CAR T-cells and when we give the CAR T-cells back so that we can control the disease and take patients into their CAR T-cells with their myeloma under control and thereby decrease the severity of complications.



Slide 74: Image

In myeloma therapy, we're a little bit ahead of lymphoma in the use of a different type of T-cell redirecting therapy which are bispecific antibodies. And these are now available for lymphoma as well, and so we're going to be using them in all of these settings.

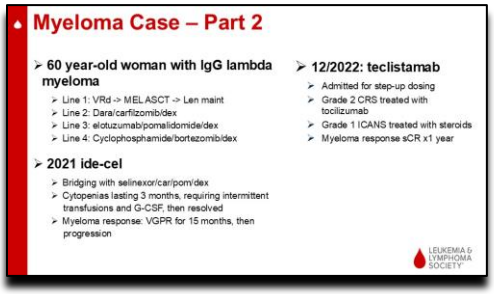
The idea is the same. It's getting the T-cell to attack the cancer cell. But instead of genetically engineering the T-cell, like on the right in CAR T-cells and putting a targeting chimeric antigen receptor that recognizes the target on the cancer cell, instead you put in a double-headed antibody where one end recognizes the target on the cancer cell; but the other end actually recognizes the CD3, the T-cell receptor on the T-cell, and so links then the T-cell to the cancer cell.

This has a couple of advantages. You don't have to collect T-cells, manufacture them, and give them back. You also don't have to give lymphodepleting chemotherapy to make room for your CAR T-cells to go in and expand. You can just take a patient and give either an IV or in most of the treatments we're using right now a subcutaneous injection

of a medication that links their T-cells to their cancer cells and get very similar effects in terms of the ability to kill cancer cells.

Listed on this slide with asterisks are our approved therapies. So, you can see on the right side, both of the approved CAR T-cells, ida-cell and cilta-cel, target B-cell maturation antigen or BCMA, which is a cell surface molecule that's very highly expressed on plasma cells and definitely on myeloma cells and very few other cells in the body, although it turns out probably on many B-cells as well. And then on the left side, you can see that two of our approved bispecific antibodies, teclistamab and elranatamab, are also targeting BCMA. And then one is targeting a different cell surface molecule, GPRC5D. That drug is called talquetamab.

And then there are other, both CAR T-cells and bispecific antibodies in development looking at other targets. And this is exciting because one of the mechanisms of resistance to therapy in multiple myeloma seems to be that cells can lose the target from their surface, and so having then treatments that can aim at different targets will allow us to get successive responses or, at some point, perhaps use different T-cell directing therapies against different targets at the same time to reduce the appearance of therapeutic resistance.



Slide 75: Myeloma Case – Part 2

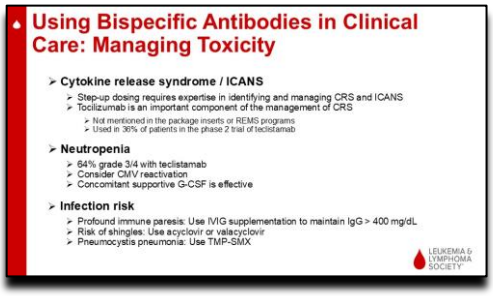
So, the same patient who we just talked about, who had gotten four prior lines of therapy and then gotten ida-cel with a selinexor bridging therapy, after her ida-cel, she had some cytopenias, some delayed cytopenias lasting about three months, needed some intermittent transfusions, and a little bit of G-CSF, which we've learned is reasonable to give in patients who have neutropenia after CAR T-cells.

Those then resolved, and she remained in a really good response for about 15 months, so beating the median progression-free survival for ida-cel by a little bit but then eventually had progression.

And so right after it was approved, in December 2022, she was admitted to get teclistamab. And the way we give bispecifics is that patients generally get admitted for step-up dosing. So we've learned that you can really reduce the severity of cytokine release syndrome by giving a really tiny dose, waiting a couple of days, then giving a bigger dose. Waiting a couple days and then giving the full dose. And by getting a very mild form of cytokine release syndrome or ICANS out of the way with a really small dose

and letting it resolve, you can then give subsequent doses without seeing recurrence of either of those toxicities.

And so in this case she had some Grade 2 cytokine release syndrome that was treated with tocilizumab, a little bit of ICANS treated with steroids, and went into a really good response, a stringent complete response that lasted for over a year.
And this is a lot of what we see with drugs like tocilizumab.



Slide 76: Using Bispecific Antibodies in Clinical Care: Managing Toxicity

So, I have a couple of slides here about using bispecific antibodies in the clinical care of patients with myeloma, and these were slides that I originally developed for tocilizumab, and so a lot of the data here are specific to tocilizumab. But the overall approach is basically the same no matter which of the bispecific antibodies you're talking about.

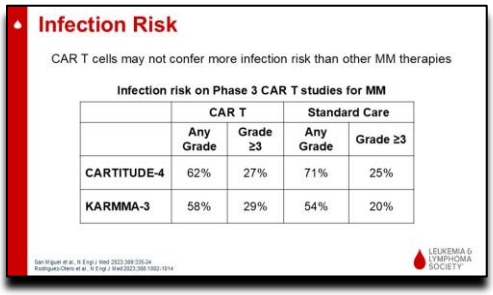
So, because there is a real risk of cytokine release syndrome and ICANS, the initial step-up dosing requires administration in a location where people have expertise in identifying and managing CRS and ICANS. And I think this is really important, because these are drugs, so you can just give a subcutaneous injection, which means anyone can give a dose of these drugs. But the toxicity profile means you really want to be confident that not just the physicians but also the nurses managing the patient really know what they're doing and can grade ICANS and recognize it and manage it and the same for cytokine release syndrome.

And although it's not mentioned in the package inserts or the REMS programs for these drugs, tocilizumab is just as important a treatment for cytokine release syndrome with bispecific antibodies as it is for CAR T-cells. And I think the reason it's not in any of the official materials is because the approval of tocilizumab for management of CRS was originally written as management of CRS from CAR T-cells. And at the time, there weren't any bispecific antibodies. They haven't gone back and updated that approval for tocilizumab, so it's just left out of a lot of the official description. But in the clinical trials of these drugs, like on the slide in the Phase 2 trial of tocilizumab, about a third of patients got tocilizumab as part of their initial step-up dosing; and so it is really important to have tocilizumab on hand wherever you're giving these treatments.

We do see a lot of cytopenias with bispecific antibodies for myeloma as well. And with tocilizumab, 64% of people had Grade 3 or 4 neutropenia at some point during their therapy. We think that's probably an inflammatory-mediated toxicity that's directly related

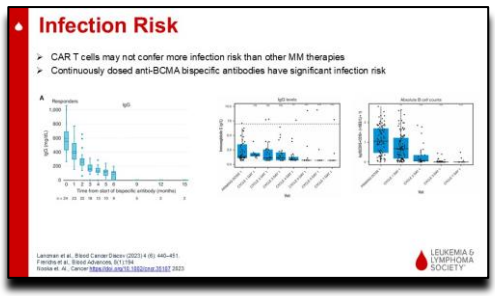
to the bispecific antibody administration. But, we should also keep in mind that there are infections that can come up that can cause cytopenias as well as concomitant medications that might cause cytopenias. We've specifically learned to consider CMV reactivation and the need to treat cytomegalovirus as part of the evaluation of severe neutropenia. We also know that you can give G-CSF in conjunction with bispecific antibodies. You can give them on the same day, and so some patients just need supportive care with ongoing G-CSF administration.

The other thing that we've learned is that especially with our BCMA-directed bispecific antibodies like teclistamab and elranatamab, the infection risk is profound. These drugs induced a really profound immune paresis and basically shut down administration, shut down production of antibodies, and patients essentially stop making any of their own antibodies. So, we routinely use IVIG supplementation to maintain an IgG level of at least 400 milligrams per deciliter. We use shingles prophylaxis with either acyclovir or valacyclovir, and we've seen enough pneumocystis pneumonia that every patient gets pneumocystis prophylaxis as well.



Slide 77: Infection Risk

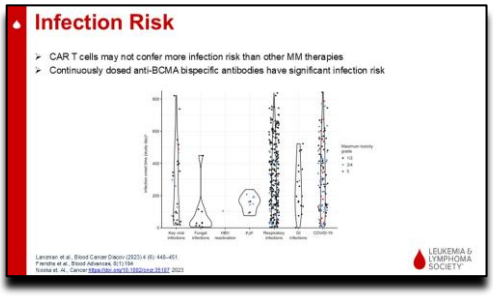
The infection risk, I think, is really important. And so CAR T-cells certainly have an infection risk, but we actually now have data from randomized trials that show that the risk of infection with CAR T-cells on the left and other standard of care therapies from myeloma, if you look at it in a randomized fashion, it actually doesn't look that different. And that's because our patients with multiple myeloma really have a relatively high risk of infections anyway. And the period of profound immunosuppression from CAR T-cells is relatively short.



Slide 78: Infection Risk

But with bispecific antibodies, these are generally continuously dosed, so patients don't just have a couple of months at the beginning. But patients, they keep getting dosing of their bispecific antibodies. You can see on the left a graph of IgG levels that go down and really get down to essentially 0 by, I think that's six months after starting treatment with a BCMA bispecific antibody. And I'm not even sure what the ones on the right are, but they essentially show actually not just that IgG levels go down, but that, also that levels of B-cells go down. And that's because BCMA's probably present on

B-cells, so you really get this very profound immunosuppression, and you see a lot of infections.

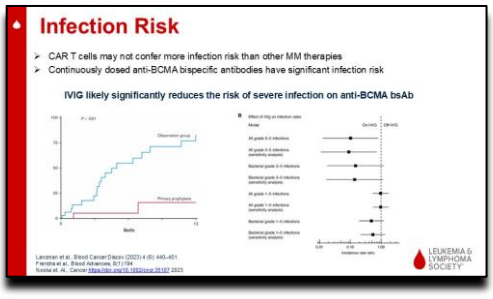


Slide 79: Infection Risk

This is a graph of different kinds of infections and the Y axis is when they occur during bispecific antibody therapy. And so fungal infections you can see generally occur very early on. Pneumocystis can occur anywhere in the first 200 days or so. And then respiratory infections and viral infections and gastrointestinal infections can kind of occur all the way throughout therapy, and you can see COVID-19 infections, including fatal COVID-19 infections happened kind of throughout bispecific antibody therapies.

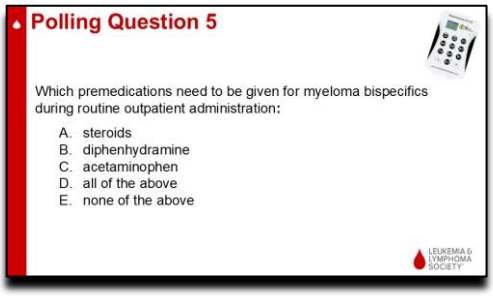
And we actually learned very early on that vaccinating patients who are on bispecific antibodies provides limited benefit because they don't generate their own antibody responses.

We also learned that measuring antibodies or serologies in patients who are on bispecific antibodies doesn't give you a whole lot of information because if you want to measure say hepatitis B antibodies, you won't find them, even if a patient previously made them. And in fact, if you find them in a patient receiving a bispecific antibody, you're much more likely to be measuring whatever was in the last dose of IVIG that they got than anything that the patient is making themselves.



Slide 80: Infection Risk

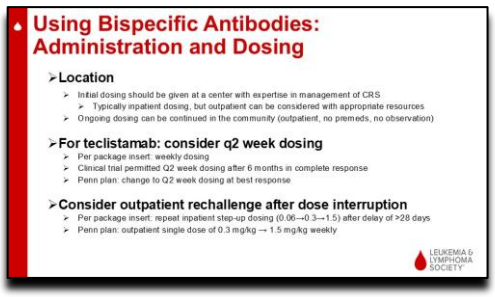
And the IVIG has really become a cornerstone of our management of infection risk in patients receiving bispecific antibodies. On the left you can see the risk of severe infections by whether patients were getting IVIG prophylaxis or just observation in blue. And you can see that the prophylaxis dramatically reduces the risk of infections; and on the right, you can see that that's primarily the severe infections that IVIG helps to prevent.



Slide 81: Polling Question

Okay, so our last polling question. "Which premedications need to be given for myeloma bispecifics during routine outpatient administration?" Is it (A) steroids, (B) diphenhydramine, (C) acetaminophen, (D) all of them, or (E) none of the above?

Okay, so 72% of you said "All of the Above" for premedications that need to be given for myeloma bispecifics during routine outpatient administration, and all of you are wrong. The people who are correct are actually the 18% who said, "None of the above."



Slide 82: Using Bispecific Antibodies: Administration and Dosing

And so, how do we give bispecifics for myeloma? I think this is really important. You know, as I said before, the initial dosing needs to be given at a location with expertise in management of CRS and ICANS. And that typically is done as an inpatient. So, the vast majority of our patients that we're treating with bispecifics are admitted. They get step-up dosing, usually every two days. So, you give an initial step-up dose, observe for 48 hours. If you see CRS or ICANS, you manage it; and then when it's resolved, you give your second step-up dose. Most of our bispecifics are using two step-up doses, and then 48 hours later you give your first full dose and then observe for 48 hours after that. And the details actually vary by product. Elranatamab doesn't require inpatient dosing for the first full dose but does for the two-step-up dosing.

We're also learning slowly that it may be safe to give these as an outpatient, but again with really careful observation. So, when we're starting just now at Penn to give these drugs as an outpatient, we're doing it with the patients coming back to our center basically every day for measurement of blood counts, kind of to check in regarding symptoms, really looking for any evidence of CRS or ICANS, and knowing that some of the patients are going to have to end up coming into the hospital through the emergency room if their CRS kicks in at 2 in the morning and they're particularly symptomatic.

And we're working on trying to figure out how to do that appropriately, but we also know that we have tocilizumab available in our outpatient infusion center. And if the patient shows up on day 3 and, to get their second step-up dose and they have a fever and they're otherwise look, appear well, or they even just have a little bit of hypotension, we can give them an outpatient dose of tocilizumab and make sure they're stabilized and then

proceed with outpatient dosing of their bispecific antibody on an ongoing basis because once they've had that initial cytokine release syndrome and gotten their tocilizumab, they're highly unlikely to ever develop that particular complication again.

And so, what's really important then is that the ongoing dosing after those initial step-up doses, for that dosing, you don't see any risk essentially of cytokine release syndrome or ICANS. And so for the long-term outpatient dosing, the side effects that you have to worry about are cytopenias and the risk of infection; and in my mind, those are the types of side effects that our community oncology practices are very used to dealing with. They're used to checking a CBC when the patient comes in and deciding can they get a dose of chemotherapy today. And they're used to thinking about risk of infection and even being able to give monthly IVIG infusions to patients at high risk of infection and make sure that they're on the appropriate antimicrobial prophylaxis.

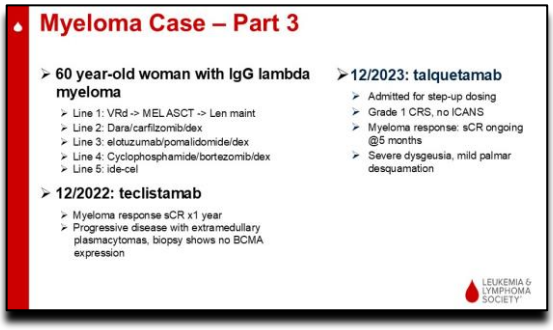
And the outpatient dosing of these drugs really is easy. As I mentioned in that polling question just now, once you get to the outpatient dosing, there are no premedications. For the initial inpatient step-up dosing, we do give premedications with steroids. I think also with diphenhydramine and acetaminophen. But once you get to the outpatient dosing, there are no premedications; and there's no post-dose observation because the patients don't get cytokine release syndrome. They don't get ICANS. So, they can come in, get their CBC. If it looks good, they get a quick subcutaneous injection and they leave. And so the outpatient dosing of bispecific antibodies is actually really generally easy.

And so I've been begging our community practices to get going with this, and a lot of people get scared because you do the REMS programs for these drugs and they're full of warnings about the severe neurotoxicity and the severe cytokine release syndrome and all that is true. But it's true only for the initial step-up dosing and the very first full dose. And so once you get past that and realize that you really can give these drugs, it's a lot more convenient for patients to get them at their local oncologist who's really close and convenient.

To try to make it even a little more convenient, we're considering giving these drugs less frequently. So, for instance, for teclistamab, which in the package insert says weekly dosing forever, I think they just updated it to do what the clinical trial did, which was every two-week dosing once they've been in a complete response for six months. But our general plan is to change to every two-week dosing once they've gotten to a good response because we know that the half-life of these drugs is very long, and the patients probably don't need to keep getting them every week.

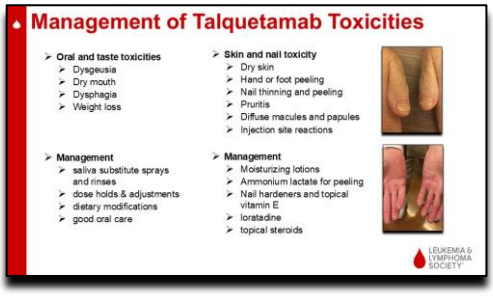
And then the other challenging situation that sometimes comes up is what happens after patients have a long treatment interruption? We had patients who needed to be off

treatment for three or four months because of, say, a severe COVID infection. And then when we wanted to restart them, we worried were we going to see cytokine release syndrome? And in general, what we found out is that if patients remain in a really good cancer response, you generally don't see cytokine release syndrome or ICANS as you start them back up again. And so although the package inserts for these drugs often recommend repeat inpatient step-up dosing, going back to the very tiny dose, medium dose, and then full dose, we generally have done our rechallenges as an outpatient using a single lower dose and then returning to the full dose; and we've done that very successfully without premedications, without observation, and not seen recurrent ICANS or CRS. And so outpatient rechallenging really is very feasible.



Slide 83: Myeloma Case – Part 3

Okay, so back to our patient. This woman who had gotten ida-cell and then gotten teclistamab with a response for about a year then had progressive disease, now with extramedullary plasmacytomas, we actually got a biopsy of one of them. Our immunohistochemical stains for BCMA are not perfect but in this case did not show any expression of BCMA, which is the target of teclistamab. And luckily for this patient, this happened at, around the time that talquetamab was first approved. And so this past December the patient was admitted for step-up dosing of talquetamab which is aimed at a different target; and then, as you can see here, had cytokine release syndrome, but only a little bit, no ICANS, and a stringent complete response going on at five months. But had some of the toxicities, which I'll show in a minute, that we see with talquetamab, which are dysgeusia and some mild, for this patient, palmar desquamation.



Slide 84: Management of Talquetamab Toxicities

And so actually, this is then the last slide in our presentation. Just say that talquetamab, which was the most recently approved bispecific for myeloma, does have some really different toxicities than the BCMA bispecifics. And the BCMA bispecifics, it's really all about infection and cytopenias in the long run. Otherwise, they're incredibly well-tolerated.

But talquetamab, which is aimed at GPRC5D has some specific toxicities. These are probably on-target toxicities because the target GPRC5D is expressed in some epithelial cells, and you can see on the right that there is some skin and nail toxicity. So dry skin,

hand or foot peeling – you can see a picture of peeling skin on the hand on the bottom there, and then nail thinning and peeling, which you can see in the top picture as well as itching, sometimes a maculopapular rash, injection site reactions.

And I would say that the skin and nail toxicity is a little bit unsightly, kind of annoying, but generally reasonably well-tolerated. And we use a lot of moisturizing lotions. You can see that some people will use things like nail hardeners. Some of the rashes can be managed with antihistamines or topical steroids. But in general, as long as you're paying attention and doing the things you would generally think about to do for these, they're not too much of a problem.

One the left side though, the oral and taste toxicities, this can be more intense. Patients can get some dry mouth and some dysphagia, but the really primary toxicity that bothers people the most is the taste alterations or dysgeusia, which can range from being just things don't taste good to things taste actively bad all the time. And so some patients really lose weight, and some patients refuse to continue on therapy with talquetamab because of that toxicity. So you have to kind of warn them. I think this happens to most people getting talquetamab. But for some people, it's really not so bad. And so it's not a reason to not try the drug. It's just a reason to think carefully about it and warn the patient ahead of time.

We've tried all sorts of things for managing the dysgeusia from talquetamab. You can see some of them listed there. They're not very effective, and so patients kind of, some patients have their dysgeusia improve slowly over time despite ongoing treatment with talquetamab. Other people, it only gets better a few months after their last dose of talquetamab; and they just have to kind of live with it as best they can during treatment. But because this targets a different target than any of our other myeloma immunotherapies, it is still getting a big place in our therapy for relapsed-refractory disease.

Okay, I think we've actually reached the end of our formal presentation.

Slide 85: Questions?

Speaker: Hello, I have a question about with the use of IVIG, have you seen a lot of reactions post-CAR T or BiTE therapies? Like your patients have hypersensitivity reactions to the IVIG?

Dr. Vogl: So, I think we do see some infusion reactions with IVIG administration. But I don't

think I have a sense that it's more after either CAR T-cells or bispecifics than what we see when we give IVIG in other situations.
01:20:25

Speaker: Hi. Quick question in the outpatient setting. We have our nurses assess the ICANS and the CRS at every visit. How long do we keep having them do that, and we have patients who've been on it for months and months?

Jessica Kassay-McAllister: So for CAR T therapy, we continue that until day 28, and then we stop.

Speaker: And what about teclistamab?

Dr. Vogl: Yes, so for bispecific antibody therapy for myeloma, I don't think you need to assess for CRS or ICANS after the first initial full dose. You know, and for teclistamab, we usually do that at our center as an inpatient dose. They're observed for 48 hours. When they come back a week later, I don't think there's any need to assess further.I guess you could ask them if they had CRS or ICANS after that first full dose, but in general that would have been seen during their hospital stay, during the 48 hours of observation. And by the time they come in, that's not one of the questions I ask my patients. Now, I can't tell you for sure what our nurses are doing in the infusion unit, but I don't think they're asking patients about CRS or ICANS because you don't see it at that point afterwards; and I think it would be a waste of time to keep asking about it.

Dr. Vogl: But asking, them whether they're, they've started on their IVIG and whether they're up to date on it and whether they're taking their acyclovir and their Bactrim, those are really good things to ask people on long-term bispecific therapies.

Dr. Shanmugasundaram: I will say on the inpatient side, it's, it probably differs from institution to institution, but we ask for an assessment every four hours when they're in that vulnerable period; and that does mean waking up the patient, unfortunately, but it's really important that we don't miss that.
Jessica Kassay-McAllister: On the outpatient side, we ask the caregiver to support us with that; and they will check it at home. They don't typically wake the patient though.

Speaker: As far as the IVIG, do you base it on levels or you just automatically go for it?

Dr. Vogl: I think right now there's probably a lot of variability in practice. So our approach at Penn has genuinely been to start people on IVIG once their IgG level falls below 400, and then pretty much dose it monthly but notice if it goes up really high and then start to think especially after CAR T-cell where some people do recover the ability to

make IgG again start to space out the doses. But I know at other centers, some places just start people immediately and dose it regardless of level because they're so impressed at how much better people do with IVIG replacement.

It's also important to mention that although most of us use intravenous immune globulin, there's also a subcutaneous immune globulin preparation available; and some centers preferentially use that which patients self-administer at home more frequently but with fewer overall reactions.

Speaker: Have you had any problems with insurance?

Dr. Vogl: With insurance approval for subcutaneous, I think often. But for IVIG for our patients after CAR T-cell and T-cell redirecting antibodies, I don't think we've seen a lot of insurance objections to it because these patients really are at high risk for infections.

Jessica Kassay-McAllister: Just to add onto that answer, for CAR T therapy, we do not initiate IVIG unless they drop below 400; and we give them two doses, and we continue to evaluate their levels. We don't continue with monthly dosing.

Speaker: Hi, so I work with mostly inpatient CAR Ts, and when we see a positive ICANS, we will start steroids. But we also initiate anakinra, and I just wanted to know if you could comment on that because it wasn't mentioned in the presentation.

Dr. Shanmugasundaram: Yeah, that's a great point. I'm sorry I didn't mention it in the PowerPoint. But yes, we will often use anakinra. Sometimes it's a case-by-case decision. If somebody's at really high risk, I'll even put them on prophylactic anakinra when they come in. And then if, it really depends on kind of the tempo of their ICANS. So, if they're heading into that Grade 3 territory, yes, no brainer. I'll put them on anakinra or increase the dose that they're already on, yep.

Speaker: Hi, my primary area is inpatient stem cell transplant; and I was just curious with both either the CAR T or with the teclistamab when we're talking about like IVIG and antibody levels and stuff, do they need to get revaccinated for different things in those instances? Or if they're on the teclistamab for a long time, when would you initiate getting revaccinated?

Jessica Kassay-McAllister: So, for the CAR T, we follow our stem cell protocol, and we revaccinate starting at three months, just as we do with our autos and our allos.

Dr. Shanmugasundaram: I have to say I think there's a paucity of data in this realm right now, and people are still looking into kind of what is the optimal vaccination schedule

and how effective certain vaccines are. But yes, we do follow our auto guidelines for now; and hopefully with more data we'll be able to figure out if that needs to change.

Dr. Vogl: And I think, you know, for CAR T-cells for myeloma, we generally do the same thing. We follow the same guidelines that we do for our autologous transplant patients. But interestingly for the bispecifics, we're, we don't really emphasize vaccination so much. I mean I still tell my patients to go ahead and get the same regular vaccines that they do during any myeloma therapy, so their annual flu shot and their pneumococcal vaccines and COVID vaccines, but I also tell them that they should get it, but that we don't really expect them to work. And what we're really doing is emphasizing the IVIG.

Speaker: Yeah. I have a question about the bispecific cost. You talked about the cost of CAR T, but with this, how does that compare up; and then with doing the incremental dosing, is there a lot of wastage of drug or is it stable where you can be able to use it if there's a lot of wastage from what you have in a vial.

Dr. Vogl: Bispecifics for, at least for myeloma, are absurdly expensive, just like most of our therapies these days. And I think four weekly doses costs on the order of $40,000 to $80,000. So, it's a really expensive treatment. I have not heard that there's a particular concern with wasting doses. I think the preparation is actually pretty easy, and I think we usually, you know, all you need is the CBC results, and then you can prep the drug and administer it. So there's very little chance that you're going to, wasting drug.

Speaker: So, it's not a weight-based dosing?

Dr. Vogl: It is right now. Yeah, 1.5 milligrams per kilogram is our standard teclistamab dose. I don't know how much left over and wasted drug that results in.

Speaker: Hi, I was wondering if any of you guys in your institutions have looked at specific to talquetamab oral cryotherapy, either before, during, or after treatment if there's any evidence or if you guys looked at that?

Dr. Vogl: So, we haven't, and I don't know if other people have. The tricky thing about our bispecifics is they have a really long half-life. So, if you were going to use cryotherapy to try to decrease say blood flow and delivery of the drug to the oral mucosa, you'd have to keep people's mouths cold for a very, very long time because the drug sticks around for weeks.

So, I'm not sure. I think it would be great if it turned out that it worked. And I'm not sure that anyone's tried. It would be always worth, you know, giving it to a couple patients and seeing what happened. But I'd be skeptical that it would be really effective.

Speaker: Is a lack of CRS response a concern for the effectiveness of either the CAR T or the bispecifics?

Dr. Shanmugasundaram: So, I think as a clinician, we're always, our Spidey sense goes up a little bit when patients don't have CRS. But the data has not really borne that out, clearly, so I can't say that a lack of CRS actually means that they're not responding. We have seen several patients who have kind of cruised through, and they still have a response, so I wouldn't say that's like a complete, "Oh, they're definitely not going to respond." But I think as a clinician, we're always a little nervous for our patients.

Speaker: Yeah.

Dr. Vogl: And in myeloma, I would say the same thing, which is we're, if somebody has no cytokine release syndrome, that worries us. But we have definitely seen amazing responses even in patients who have absolutely zero cytokine release syndrome. So, you can reassure a patient who's sitting in front of you freaking out because it's day ten after their CAR T-cells and they haven't have a fever and say that doesn't mean that you're not going to have a response.

Speaker: Yeah, I just had a quick question about the bispecific versus the CAR T therapy. Is it one or the other, and how do you make that decision about who gets what?

Dr. Shanmugasundaram: A lot of patients who have refractory-relapsed lymphoma are candidates for both, and some patients will get both. So, it's not that one will preclude you from getting the other. In the lymphoma world, I will say that, you know, because bispecifics are relatively new, we don't have as much long-term data as we do for the CAR T-cell therapy. And as we mentioned earlier, we see CAR T-cells as providing potentially a curative therapy for our patients, so I do see that a lot of patients are referred for CAR T-cell therapy first as a consideration to look for that cure as opposed to the bispecifics, which we just don't really know whether they can offer that same type of cure, that ability to cure just yet. So, oftentimes they'll come in for CAR T first before they go on for bispecifics.

The way that it happens the other way around is if we can't get the disease under control for CAR T-cell therapy, then we'll sometimes use the bispecific as a bridge.

Dr. Vogl: And I think for multiple myeloma, we, it ends up being a similar approach. We don't think we're curing any of our myeloma patients with either CAR T-cells or bispecifics. But the data for the CAR T-cells are a little bit more mature and seem to maybe, in some situations, have longer median progression-free survival. So I think for younger patients

or patients who we think are in a good enough response or will be able to get a good enough response with bridging therapy, we tend to favor CAR T-cells. But we actually don't know which are the best, and there are increasing data on giving CAR T-cells after a bispecific and seeing good responses and/or giving a bispecific after CAR T-cells. And so right now we're not assuming that we're going to restrict patients to getting one or the other.

And the comparative trials as to which ones are better are still to be done, and we're also trying some strategies where we're giving both, either bispecifics during bridging to allow us to get to CAR T-cells or bispecifics as consolidation after CAR T-cells. And that's kind of intriguing, expensive, and complicated, but intriguing and maybe the way of the future.

Speaker: I work at like a smaller community hospital, so we don't give CAR T, but every once in a while we'll have a patient come in through our doors that, you know, just went through treatment and I wasn't able to catch the whole presentation. I came in late, but other than the pamphlets and stuff, in terms of like educating our floor staff about how to better manage these patients, what would you think the best place would be for me to start?

Jessica Kassay-McAllister: I think you could reach out to an institution that does treat CAR T patients, and they could probably help provide you with some education. Like our institution would be willing to help with that.
01:33:30

Jessica Kassay-McAllister: So, you can look me up and reach out to me.

Speaker: Okay.

Dr. Vogl: And the Cartox app that's listed in the presentation is actually pretty cool. And as a way of kind of looking through and seeing what you would do in different situations I think could be very useful.

Speaker: Exactly. Okay, awesome, thank you.

Jessica Kassay-McAllister: But please do reach out.

Slide 86: Thank You!

Lauren Berger: Thank you to our faculty, and thank you so much for staying and asking such great questions. Have a great day.