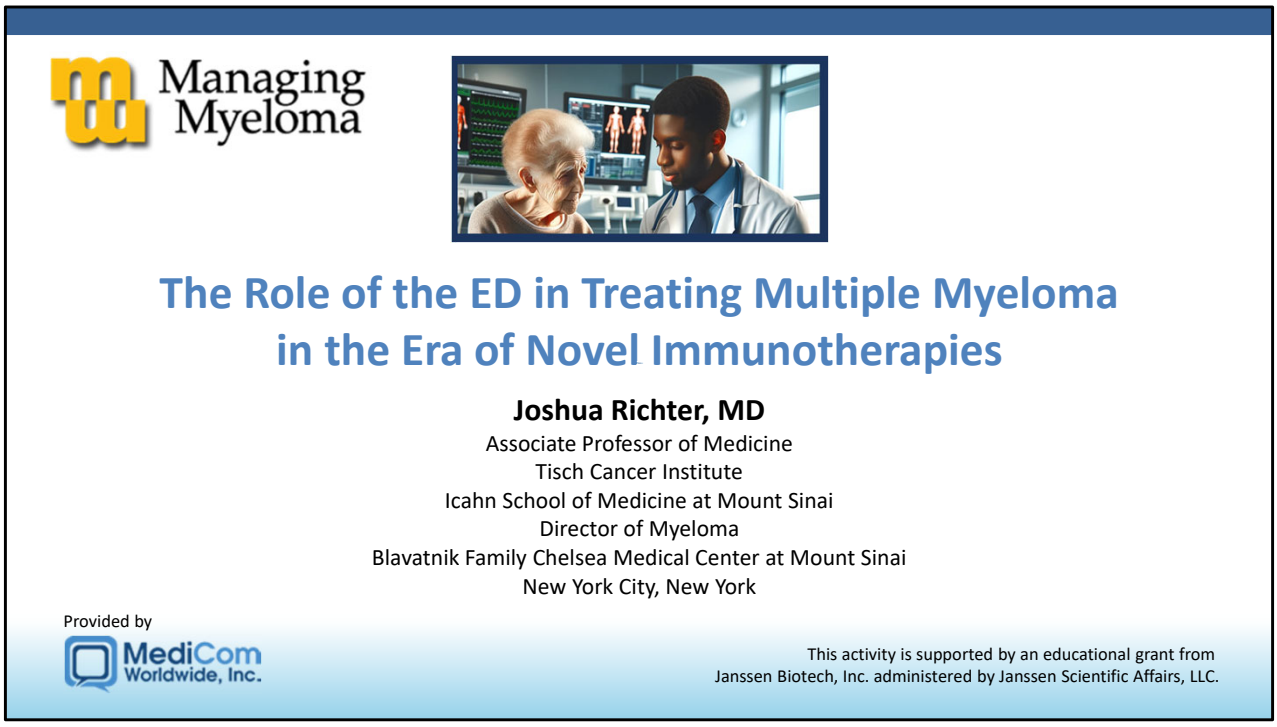
The Role of the ED in Treating Multiple Myeloma in the Era of Novel Immunotherapies



Moderator: Hello, and welcome to our accredited presentation entitled *The Role of the ED in Treating Multiple Myeloma in the Era of Novel Immunotherapies*. Today's program is provided by MediCom Worldwide, Inc. and is supported by an educational grant from Janssen Biotech, Inc. administered by Janssen Scientific Affairs, LLC.

It is now my pleasure to turn this program over to Dr. Joshua Richter, Associate Professor of Medicine, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, Director of Myeloma, Blavatnik Family Chelsea Medical Center at Mount Sinai in New York, New York. Dr. Richter, the floor is yours.

Dr. Richter: Thank you so much. And one of the best parts about that title is listening to people's struggles to say Blavatnik. You actually did amazing, but I do apologize for that.

Well, thank you everyone for tuning in today, both live and virtual. Apologies that I'm not there. I did my undergrad in Baltimore, and I am a big fan of the city.

Today we're going to be talking about *The Role of the Emergency Department in Treating Multiple Myeloma in the Era of Novel Immunotherapies.*

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It is a really exciting topic and this was developed in concert with a number of amazing physicians including one of my colleagues, Dr. Larysa Sanchez, and perhaps the greatest emergency room doctor I've ever met, Dr. Monica Wattana.

Faculty Disclosures

- **Dr. Joshua Richter,** faculty for this educational activity, has relevant financial relationships to disclose related to speakers' bureaus from Adaptive Biotechnologies, Bristol Myers Squibb Company, Janssen Pharmaceuticals, Inc., and Sanofi; and for consulting and advisory activities from AbbVie Inc., Bristol Myers Squibb, Genentech, Inc., Janssen, Karyopharm Therapeutics, Pfizer Inc., Sanofi, and Takeda Oncology.
- **Dr. Larysa Sanchez,** content contributor for this educational activity, has relevant financial relationships to disclose related to consulting and advisory activities from Janssen Pharmaceuticals, Inc.
- **Dr. Monica Wattana,** content contributor for this educational activity, has disclosed no relevant financial relationships with any ineligible company (commercial interest).

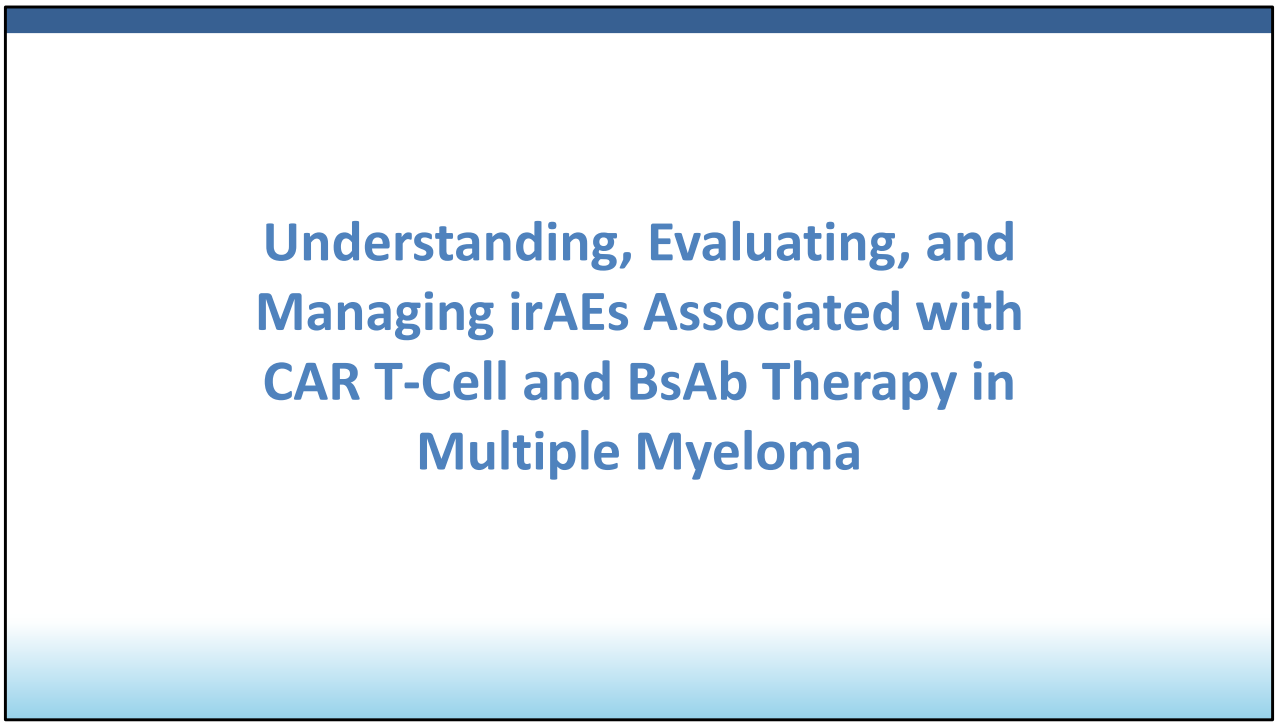
All relevant financial relationships listed for these individuals have been mitigated prior to this activity.

Here are our disclosures. We have a number of them. They're all listed below.

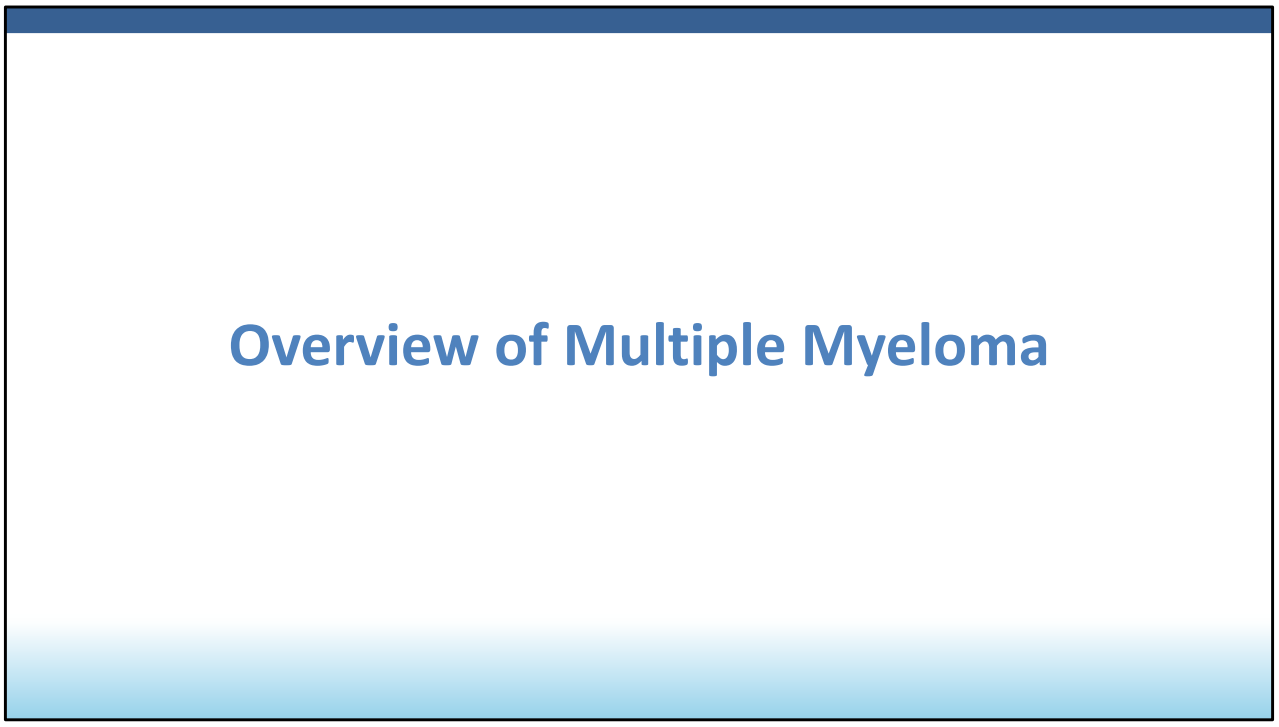
Learning Objectives

- Identify currently available and emerging classes of novel immunotherapies for relapsed or refractory multiple myeloma (RRMM), focusing on CAR T-cell therapies and bispecific antibodies (BsAbs)
- Identify known treatment-related adverse events (TRAEs) associated with CAR T-cell therapies and BsAbs in RRMM patients which have the potential to be seen in the Emergency Department (ED)
- Correlate the incidence and prevalence of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) with the impact of these MM-related TRAEs
- Outline practical, applied strategies and available tools that may be used to guide ED clinicians in promptly recognizing and escalating care of MM treatment-related CRS and ICANS

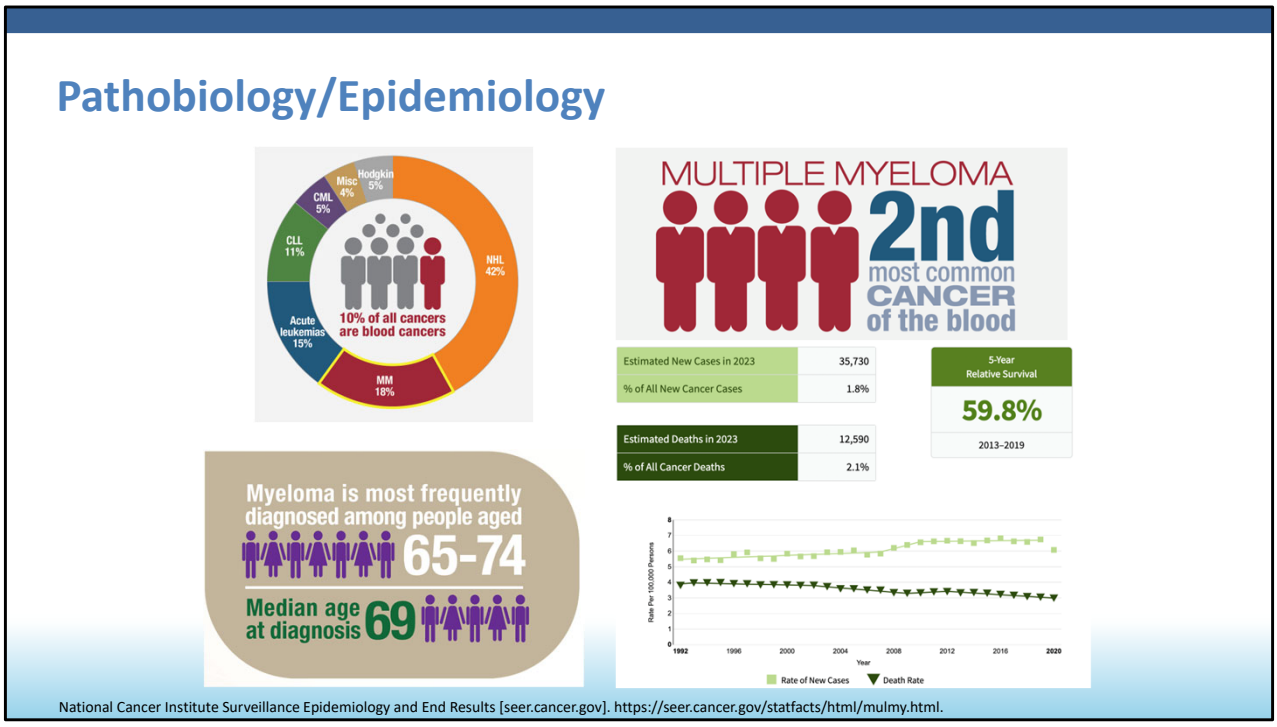
Our learning objectives. We are going to be discussing the latest and greatest in myeloma therapy. Really when we are talking about the latest and greatest, we are talking about the immune therapies, the T-cell redirection therapies, basically bispecific antibodies and CAR T-cell therapies. And although these drugs have brought with them some of the greatest response rates, most durable remission rates we've ever seen in myeloma, they come with a variety of novel adverse events and the reality is these patients are going to be showing up in our Emergency Departments, and special considerations need to be taken and more collaboration now than ever between our emergency room colleagues and our hem/onc colleagues.



So really discussing some of the nitty gritty with particular focus on some of the main immune-related adverse events such as cytokine release syndrome, or CRS and the immune effector cell-associated neurotoxicity syndrome, or ICANS.



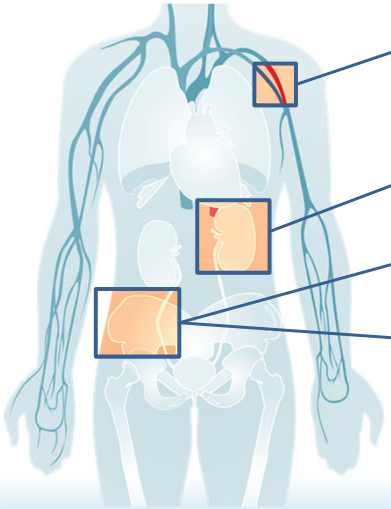
So, let's dive right in and talk about some of the basics, an overview of myeloma.



Myeloma is considered the second most common cancer of the blood. Non-Hodgkin's lymphoma is number one, but let's be honest, they cheat. They have all these different types, diffuse large B, mantle cell, marginal zone, follicular. Myeloma is number one, but for the purposes of this discussion, we'll call it number two. It's about 1.8% of all cancer diagnoses in the US. About 10% of all blood cancers. The average age is 69 years and it does increase in frequency with advancing age.

Over the last several decades, we have seen phenomenal improvements, in progression-free and overall survival. If we date back to the 1970s and 80s, the median overall survival, all comers from diagnosis to death is about 2 years. Now we can see here in some of the most recent SEER data, the 5 year survival rate from patient’s diagnosed between 2013 to 2019 is almost 60%, so we have many patient’s having overall survivals of greater than a decade being diagnosed in the modern era.

Effects of Myeloma and Common Symptoms



Low blood counts
- Anemia is present in 60% of patients at diagnosis
- May lead to anemia and infection

→ Weakness, Fatigue, Infection

Decreased kidney function
- Occurs in over half of myeloma patients

→ Weakness

Bone damage
- Affects 85% of patients
- Common sites include spine, pelvis, and ribs
- Leads to fractures

→ Bone pain

Bone turnover
- Leads to high levels of calcium in blood (hypercalcemia)

→ Loss of appetite, Weight loss

About 10% to 20% of patients with newly diagnosed myeloma will not have any symptoms.

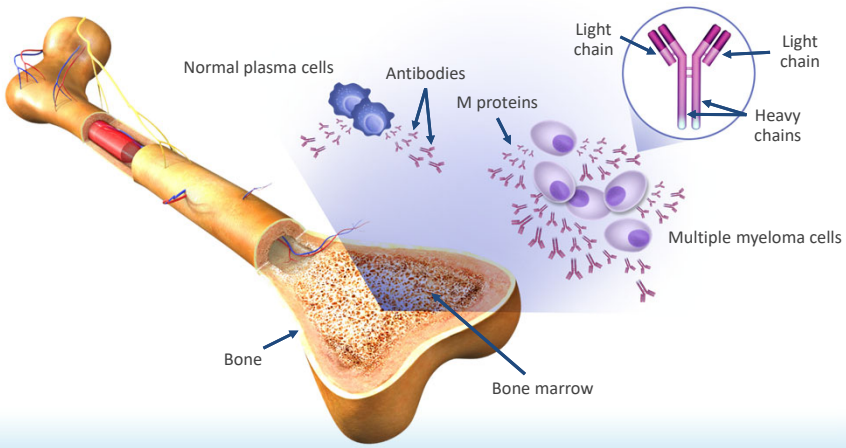
Multiple Myeloma Research Foundation (MMRF) [www.themmrf.org]. Accessed April 14, 2016. Last updated 2023. https://themmrf.org/multiple-myeloma.
Campbell K. *Nurs Times*. 2014;110:12.

Now when we find monoclonal gammopathies or an M spike in the blood, it is not always myeloma. There are a variety of other conditions we can consider, including more benign ones like MGUS, the monoclonal gammopathy of undetermined significance. But when myeloma does evolve to require therapy, the common symptoms fall under the acronym CRAB and the CRAB symptoms are what we've been talking about for decades.

So C for high calcium levels. When the calcium levels go up you can have kidney issues, you can have confusion or pain. R for renal, another word for kidney. The kidney is like a filter for the blood and when you have too much bad protein floating around it clogs up the filter. You can have kidney dysfunction. A for anemia, we normally have red blood cells made in our bone marrow, but if you have malignant processes inside that are growing and growing, it's going to crowd out the healthy cells and your blood counts will drop and you can get anemia. And yeah, B for bone lesions, you can get the lytic lesions or holes in the bones from increased osteoclast activity. And ultimately, besides pain, these patients can present with fractures.

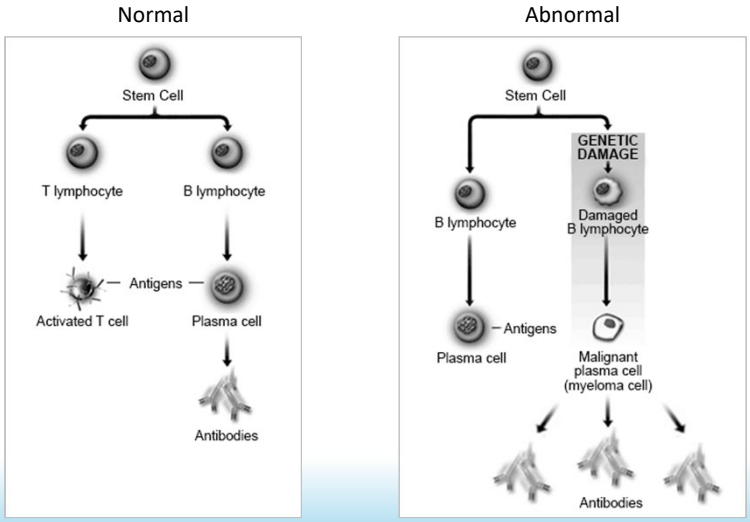
What's really important to note is that 10 to 20% of all myeloma patients are diagnosed with no symptoms. A common presentation is a patient goes into their PCP for yearly blood work. It shows an elevation in their total protein. They undergo further workups, are sent to a hematologist/oncologist and are diagnosed with an incurable malignancy with not a single symptom.

What Is Multiple Myeloma?



So in 2024, we have evolved our understanding of both diagnostics and therapeutics in the cancer world. We know tons about genomics, proteomics and immunologics. But really we define a cancer, we define a malignancy based on what cell became malignant. A lung cell becomes malignant, that's lung cancer. A skin cell becomes malignant, that's melanoma.

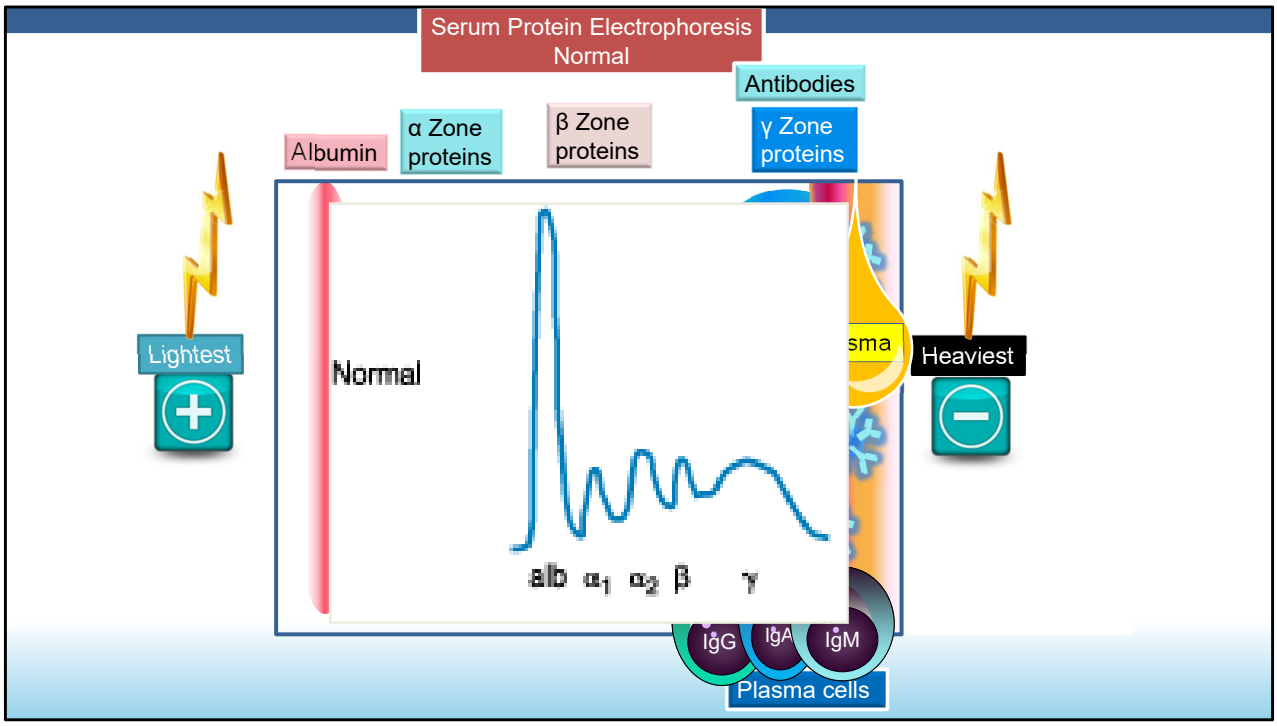
Normal vs Abnormal Plasma Cells



Adapted from Multiple Myeloma Research Foundation.

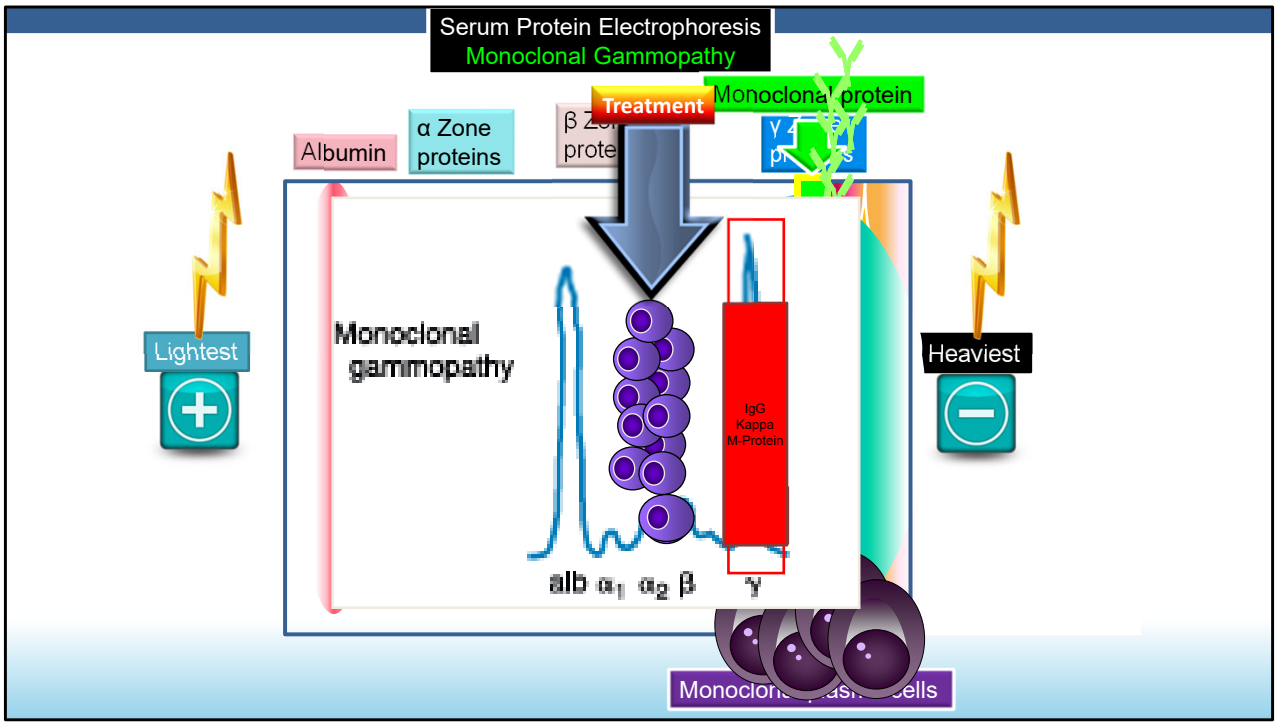
Myeloma is a malignancy of plasma cells, and plasma cells are immune cells that make antibodies to fight infection.

And normally when we talk about the differentiation of hematopoietic cells, we start with our stem cell which gives rise to B lymphocytes and plasma cells are simply terminally differentiated B lymphocytes. When they become rogue or malignant, they start, instead of making healthy antibodies, they make misfolded proteins and that's that M protein.



So, when we want to look for proteins, normal or abnormal, we use a serum protein electrophoresis. Really cool technology where we basically take the patient's plasma, put it on electrophoretic plate and zap it with some electricity. And when we zap it, we actually see the proteins kind of allude out, based from heaviest to lightest in different zones.

And basically, all the proteins in the body are either albumin or globulins. Globulins come as alpha1, alpha2, beta, and gamma. Gamma is where the antibodies live, and normally this should be polyclonal. You should have all different types of plasma cells making different antibodies to fight the flu, COVID, syphilis, whatever, and that's what we see in normal circumstances. We call this polyclonal, you can see that gamma region is low and hooked.



But what happens when we find a monoclonal gammopathy? We go through the same process, we put the patient's plasma on the electrophoretic plate, we zap it and now when we see the proteins allude out albumin, alpha and beta are typically normal. In the gamma zone we see a monoclonal spike, a group of protein that really all comes from the same cell, not from different cells, not polyclonal meaning many, but monoclonal meaning one because the cells are all related to one another.

Ultimately this looks like a big spike or that M spike, it used to be called positive cathedral sign and this shows that the bad protein is being made by the malignant plasma cells. Now we associate this with the amount of plasma cells and this is how we monitor the disease, where we find someone with one of these disorders, we administer some type of treatment which kills the bad cells in the marrow, leading to a lower amount of protein in the blood.

Diagnostic Criteria (SLiM-CRAB)

- Clonal bone marrow plasma cells > 10%, bony or extramedullary plasmacytoma with any of the following myeloma-defining events
- End organ damage attributable to myeloma (CRAB)
  - C Hypercalcemia: Ca++ > 0.25 mmol/L above upper limit of normal
  - R Renal insufficiency: creatinine > 2 mg/dL or eGFR < 40 mL/min
  - A Anemia: Hgb > 2 g/dL below the lower limit of normal
  - B Bone lesion: one or more osteolytic bone lesions on X-ray, CT, PET-CT
- Biomarkers of malignancy
  - Clonal bone marrow plasma cells > sixty (60%)
  - Involved:uninvolved serum free light chain ratio > 100:1
  - > 1 focal bone lesion on MRI of at least 5 mm (not same thing as lytic lesion)

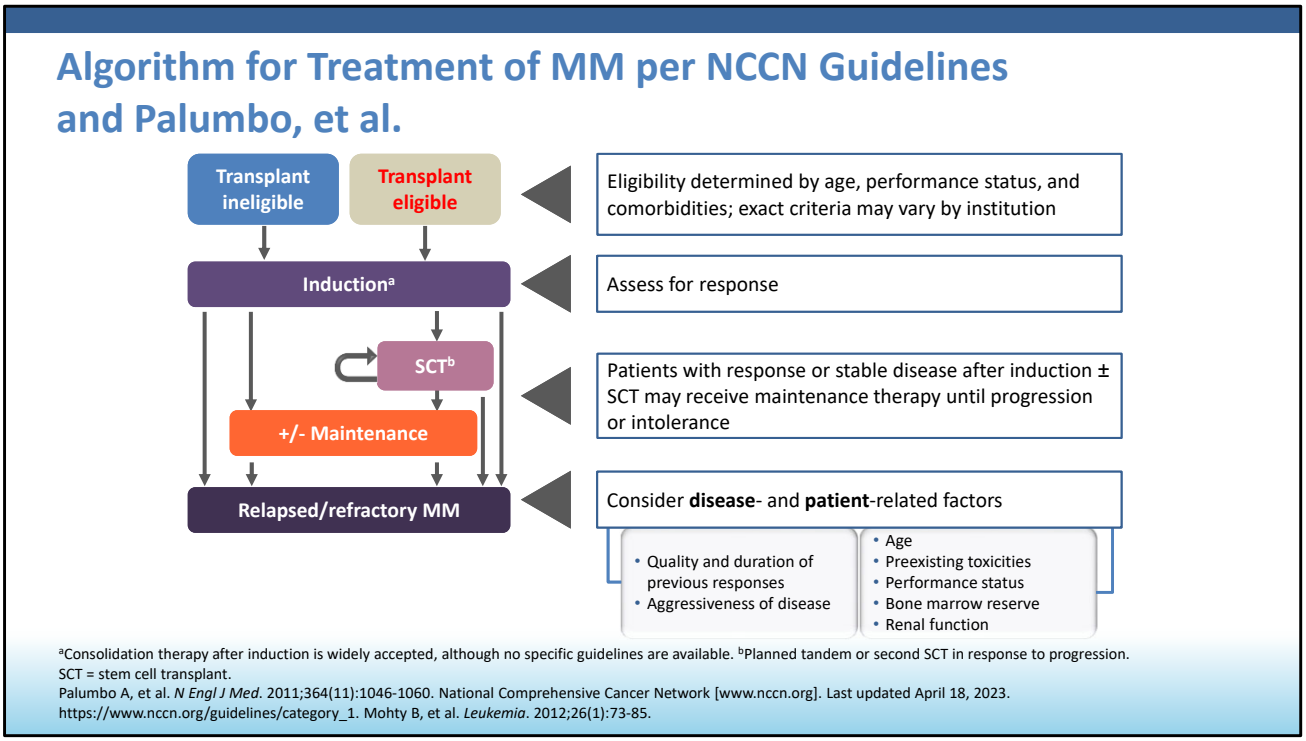
Ca = calcium; Hgb = hemoglobin; eGFR = estimated glomerular filtration rate; CT = computed tomography; PET-CT = positron emission tomography-computed tomography; MRI = magnetic resonance imaging. SLiM = S (greater than or equal to sixty percent clonal plasma cells in the bone marrow), Li (involved/uninvolved free light chain ratio of 100 or more with the involved FLC being greater than or equal 100 mg/L), M (MRI with more than one focal marrow lesion).

Now the CRAB symptoms have been the standard of care for many years although we now have begun to understand that people with earlier disorders, more benign versions like MGUS or smoldering myeloma. Smoldering myeloma is where you have the myeloma protein and you have the bad cells, but no symptoms, no CRAB symptoms and standard procedure was to monitor these patients without treatment. However, we now recognize that there are certain predictors that patients may have, that even though they don't have symptoms we want to consider treating them.

We like to say that CRAB has gone on a diet and now we call it the SLiM-CRAB criteria. So if you have either more than 3 grams of the bad protein in the blood, or more than 10% of the bad cells in the marrow, and you have no CRAB, we used to not treat you. Now if you have S for sixty, so more than 60% plasma cells in the bone marrow, Li for light chain ratio, so a kappa to lambda or lambda to kappa serum ratio of greater than 100:1, or B for bone lesion. We used to talk about bone lesions on x-rays, now if you have greater than one bone lesion of at least 5 mm seen on an MRI we consider treating you. So ultimately, we don't have to treat patients with the SLiM criteria, but we have the option to in some of those people that may be borderline, and may truly warrant therapy.

MM Treatment Guidelines

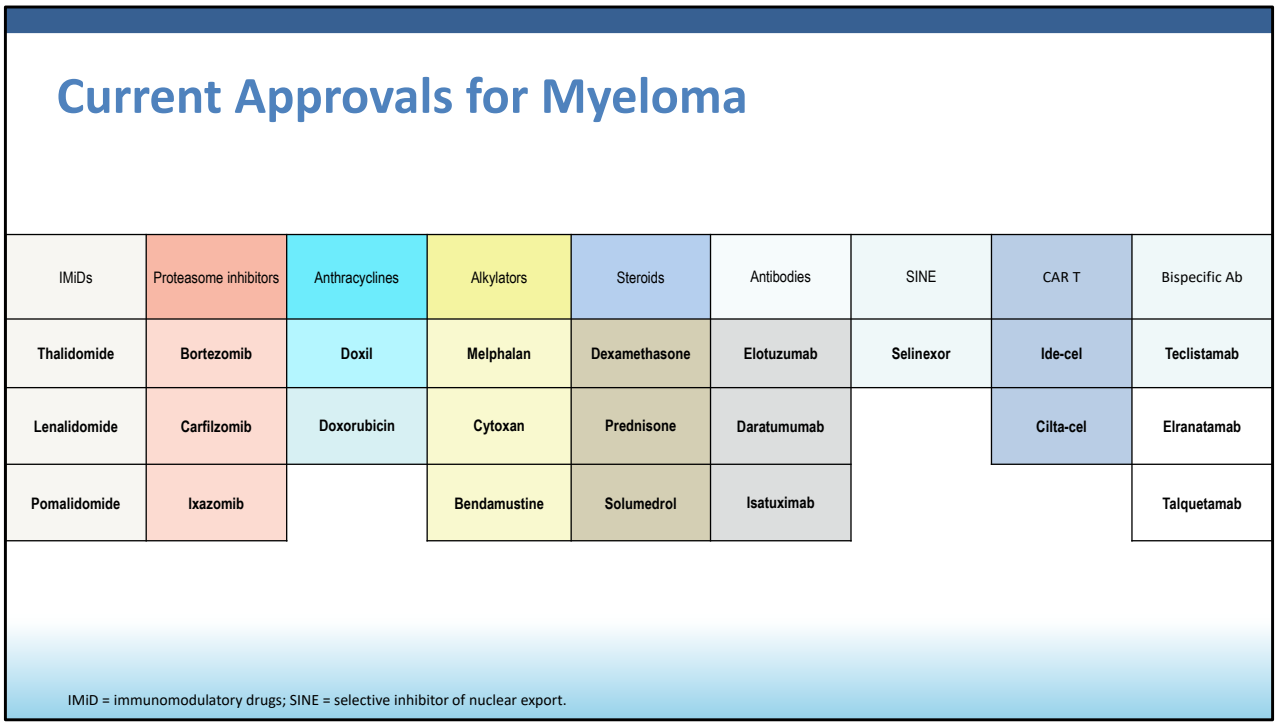
So what are the current treatment guidelines?



So even though the specific drugs that we use have changed dramatically across the years, the general scheme of how we approach newly diagnosed myeloma has not. In general, when we diagnose patients as needing treatment, we term them transplant eligible or transplant ineligible.

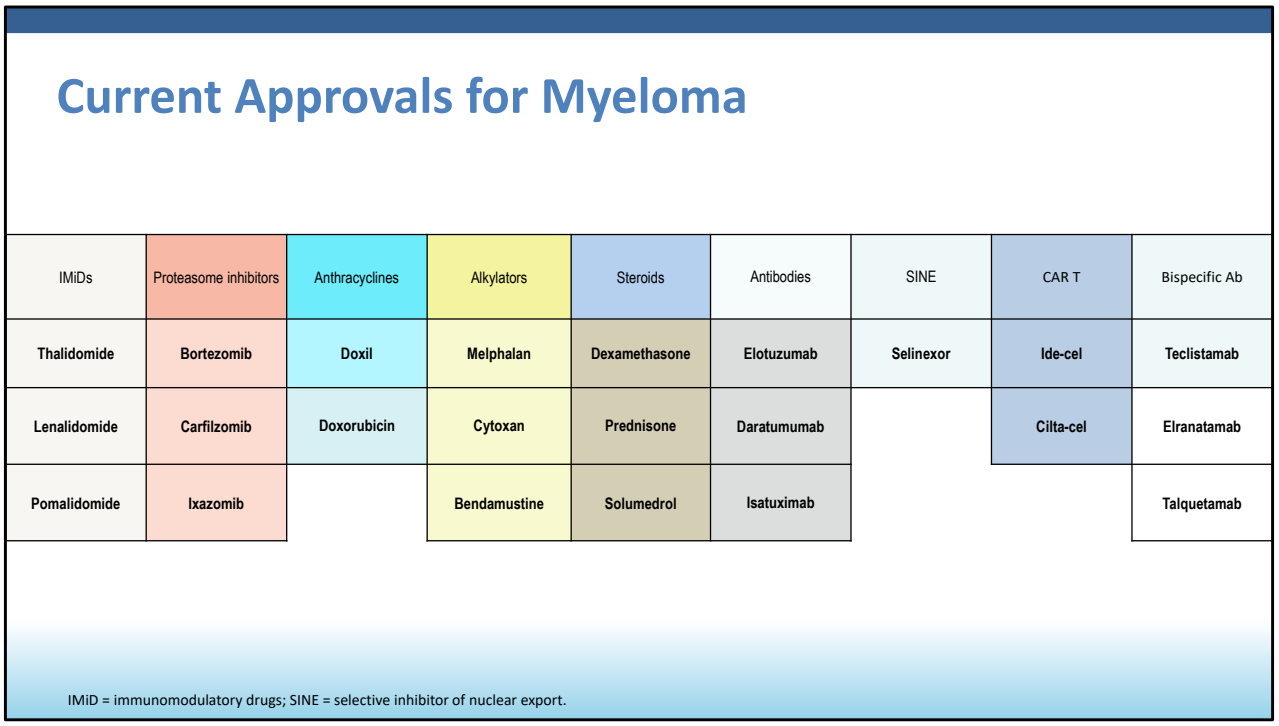
Here the term transplant refers to an autologous stem cell transplant. Now it's not an allogeneic transplant, it's simply administering a high dose of melphalan, which kills both healthy and abnormal cells, but rescuing the bone marrow with autologous previously collected peripheral blood stem cells. Now, there are no hard and fast guidelines in the United States of who is transplant eligible and who is transplant ineligible. Suffice it to say that other countries have guidelines. In the US we refer to the eligible patients as the younger and fitter group with the ineligible patients being older and frailer, but again, a lot of this is in the eye of the beholder.

Either way, all patients receive some type of induction therapy. The transplant eligible patients will receive high-dose chemotherapy with autologous stem cell rescue. All patients tend to go on some type of long-term maintenance therapy. But ultimately, regardless of which drugs you use, transplant or not, two drugs, three drugs, four drugs, fancy drugs, old drugs, everyone really ends up in the bucket of relapsed and refractory disease.



And this is the current landscape that we look at for the relapsed/refractory world. We have a lot of different drugs at our disposal. We start off with the classical IMiD drugs, the immunomodulatory drugs. These are all derivatives of thalidomide. So for those of you that remember thalidomide from the 1950s and 60s, that was used to help pregnant women with morning sickness, and sleep, because it didn't suppress respiratory centers like the barbiturates would. Unfortunately, it caused deformities in the limbs through a variety of mechanisms, including inhibition of vascular endothelial growth factor.

It turns out that those classes of agents actually have significant anti-myeloma activity, not just through inhibition of VEGF within the marrow space, but additionally through propogating pro-apoptotic mechanisms. Mostly they modulate NK T cells, so that’s why they are called IMiDs. We have thalidomide, lenalidomide, and pomalidomide. We have the proteasome inhibitors. Remember that the proteasome ubiquitin pathway is where the garbage disposal system of cells. And because myeloma cells make tons of that M protein, that tons of garbage, they are really targeted to myeloma cells.



We have classical chemo drugs that we've used across a variety of tumor types, including anthracyclins and alkylators. Steroids have become a mainstay of most of our therapies. And now on the right we have some of our newer, cooler medicines including these monoclonal antibody drugs like elotuzumab, daratumumab, and isatuximab, as well as our SINE, our selective inhibitor of nuclear export selinexor.

What we are really going to focus on today are the last 2 columns where we've moved on from classical chemotherapy to some of the newer drugs, and now on to the T cell redirection where the goal is not just to kill all the good and the bad, but really to push up the good cells to attack the bad. We really have 2 modalities the CAR T cell, CAR T standing for chimeric antigen receptor T cells. At the time of this recording we have 2 FDA approved ones, ide-cel and cilta-cel. And the off-the-shelf bispecific antibodies. At the time of this recorded we have 3 FDA approved ones, teclistamab, elranatamab, and talquetamab.

NCCN Guidelines: Initial Therapy | Transplant Eligible

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES[a-d]
Preferred Regimens • Bortezomib/lenalidomide/dexamethasone (category 1) • Carfilzomib/lenalidomide/dexamethasone[k]
Other Recommended Regimens • Daratumumab/lenalidomide/bortezomib/dexamethasone
Useful In Certain Circumstances • Bortezomib/cyclophosphamide/dexamethasone[e] • Bortezomib/doxorubicin/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone[e,f,k] • Daratumumab/bortezomib/thalidomide/dexamethasone • Daratumumab/bortezomib/cyclophosphamide/dexamethasone • Daratumumab/carfilzomib/lenalidomide/dexamethasone[k] • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib[g] (VTD-PACE) • Isatuximab-irfc/lenalidomide/bortezomib/dexamethasone

MAINTENANCE THERAPY
Preferred Regimens • Lenalidomide[h] (category 1)
Other Recommended Regimens • Bortezomib
Useful In Certain Circumstancesz • Bortezomib/lenalidomide[j] • Carfilzomib/lenalidomide[j] • Daratumumab ± lenalidomide[j] • Ixazomib (category 2B)[i]

Now in terms of how we approach myeloma in terms of the general therapy, here we can see the NCCN Guidelines. For the most part our initial therapy is really where we distinguish transplant eligible from ineligible. Once patients end up in the relapsed/ refractory setting we don't distinguish one from the other. Again, we may want to reserve certain drugs for fitter patients, but overall, there's no purely accepted schema.

For patients who are transplant eligible, in general we tend to use either 3 or 4 drug regimens with some of the more common regimens including bortezomib, lenalidomide, and dexamethasone, plus or minus the addition of the monoclonal antibody, daratumumab.

NCCN Guidelines: Initial Therapy | Transplant Ineligible

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES[a-d]	
Preferred Regimens • Bortezomib/lenalidomide/dexamethasone (category 1) • Daratumumab/lenalidomide/dexamethasone (category 1)	
Other Recommended Regimens • Daratumumab/bortezomib/melphalan/prednisone (category 1) • Carfilzomib/lenalidomide/dexamethasone[k]	• Daratumumab/cyclophosphamide/bortezomib/dexamethasone
Useful In Certain Circumstances • Lenalidomide/low-dose dexamethasone (category 1)[m] • Bortezomib/cyclophosphamide/dexamethasone[e] • Bortezomib/dexamethasone	• Bortezomib/lenalidomide/dexamethasone (VRD-lite) for frail patients • Carfilzomib/cyclophosphamide/dexamethasone[f,k] • Lenalidomide/cyclophosphamide/dexamethasone

MAINTENANCE THERAPY
Preferred Regimens • Lenalidomide (category 1)
Other Recommended Regimens • Bortezomib
Useful In Certain Circumstances • Bortezomib/lenalidomide[j] • Ixazomib (category 2B)[i]

When it comes to non-transplant eligible, the two most common regimens are listed at the top, bortezomib, lenalidomide, and dexamethasone or daratumumab, lenalidomide, dexamethasone. Both extremely efficacious regimens, high response rates and very durable.

NCCN Guidelines: Early Relapse (1-3 Prior Therapies)

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,n-o,q] Relapsed/Refractory Disease After 1–3 Prior Therapies	
Preferred Regimens *Order of regimens does not indicate comparative efficacy*	
Bortezomib-Refractory[p]	**Lenalidomide-Refractory[p]**
• Carfilzomib/lenalidomide/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Daratumumab/lenalidomide/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone *After one prior therapy including lenalidomide and a PI* ‣ Daratumumab/pomalidomide/dexamethasone (category 1) *After two prior therapies including lenalidomide and a PI* ‣ Isatuximab-irfc/pomalidomide/dexamethasone (category 1)	• Daratumumab/bortezomib/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Pomalidomide/bortezomib/dexamethasone (category 1) • Selinexor/bortezomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone • Elotuzumab/pomalidomide/dexamethasone *After one prior therapy including lenalidomide and a PI* ‣ Daratumumab/pomalidomide/dexamethasone (category 1) *After two prior therapies including lenalidomide and a PI* ‣ Isatuximab-irfc/pomalidomide/dexamethasone (category 1) *After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy* ‣ Ixazomib/pomalidomide/dexamethasone

PI = proteasome inhibitor.

When it comes to relapsed/refractory myeloma, we really refer to the relapse space either being early relapse or late relapse. Early relapse is 1 to 3 prior lines of therapy, late relapse is 4 or more prior lines of therapy.

Now, there are no clear guidelines about what drug to use and in what circumstance. In myeloma we talk about 3 modalities of picking a therapy: disease related factors, patient related factors, and treatment related factors. So patient related–is the patient old or young, fit or frail. What comorbidities do they have? Disease related factors–is the disease growing fast, or slow. Is there extramedullary disease, bad cytogenetics, functionally high risk? But ultimately, one of the first passes we use is treatment-related factors. What drugs have they had before, what have they not had before? So what are they naive to, what are they refractory to, what are they sensitive to? The NCCN Guideline follows this by dividing patients into being bortezomib refractory, or lenalidomide refractory. In the United States and in many other countries, the majority of people in early relapse are lenalidomide refractory. So we are mostly looking at a lot of our regimens that include CD38 targeting monoclonal antibodies like daratumumab and isatuximab.

NCCN Guidelines: Early Relapse (1-3 Prior Therapies)

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,n-r] Relapsed/Refractory Disease After 1–3 Prior Therapies	
Other Recommended Regimens	
• Carfilzomib (twice weekly)/dexamethasone (category 1) • Elotuzumab/lenalidomide/dexamethasone (category 1) • Ixazomib/lenalidomide/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone • Daratumumab/cyclophosphamide/bortezomib/dexamethasone • Elotuzumab/bortezomib/dexamethasone • Ixazomib/cyclophosphamide/dexamethasone • Lenalidomide/cyclophosphamide/dexamethasone	*After two prior therapies including an IMiD and a PI and disease progression on/within 60 days of completion of last therapy* ‣ Pomalidomide/cyclophosphamide/dexamethasone
Useful in Certain Circumstances	
• Bortezomib/dexamethasone (category 1) • Bortezomib/liposomal doxorubicin/dexamethasone (category 1) • Lenalidomide/dexamethasone (category 1) • Carfilzomib/cyclophosphamide/thalidomide/dexamethasone • Carfilzomib (weekly)/dexamethasone • Selinexor/carfilzomib/dexamethasone • Selinexor/daratumumab/dexamethasone • Venetoclax/dexamethasone ± daratumumab or PI only for t(11;14) patients	*After two prior therapies including IMiD and a PI and with disease progression on/within 60 days of completion of last therapy* ‣ Pomalidomide/dexamethasone (category 1) ‣ Ixazomib/pomalidomide/dexamethasone ‣ Selinexor/pomalidomide/dexamethasone *For treatment of aggressive MM* ‣ Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP) ‣ Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE) *After at least three prior therapies including a PI and an IMiD or are double-refractory to a PI and an IMiD* ‣ Daratumumab

We have a laundry list of other options to use which include some of our old drugs, and some of our new drugs, and even some selected out regimens for patients with an 11;14 translocation. We use a drug called venetoclax.

NCCN Guidelines: Late Relapse (> 3 Prior Therapies)

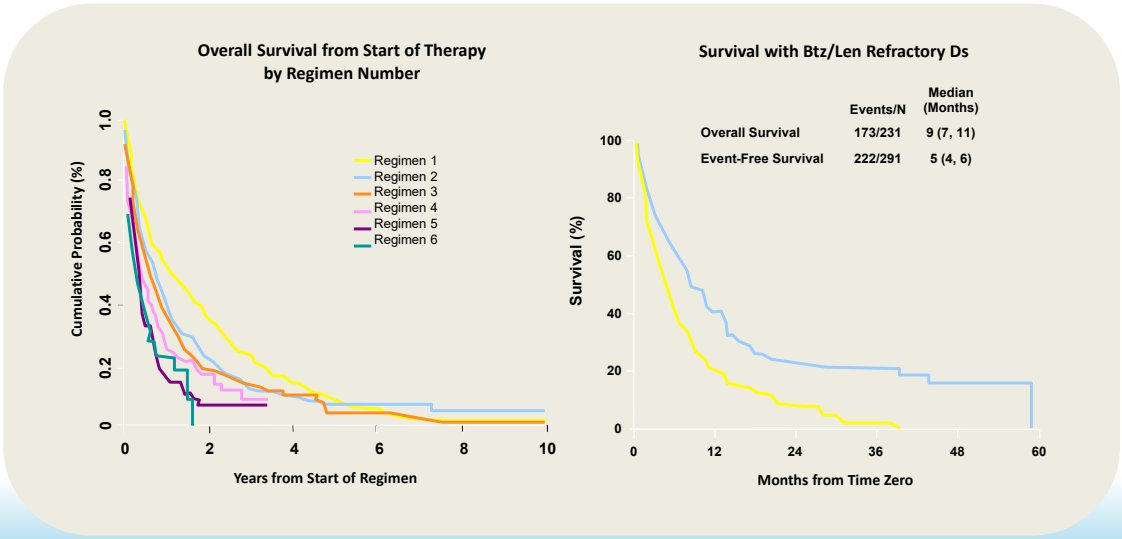
THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,n-o] Relapsed/Refractory Disease After 3 Prior Therapies
Preferred Regimens
After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD[s] ▸ *CAR T-cell Therapy*: ◊ **Ciltacabtagene autoleucel** ◊ **Idecabtagene vicleucel** ▸ *Bispecific Antibodies* ◊ **Elranatamab-bcmm** ◊ **Talquetamab-tgvs** ◊ **Teclistamab-cqyv**
Other Recommended Regimens
• **Bendamustine**[t] • **Bendamustine/bortezomib/dexamethasone**[t] • **Bendamustine/carfilzomib/dexamethasone**[t] • **Bendamustine/lenalidomide/dexamethasone**[t] • **High-dose or fractionated cyclophosphamide** *After at least four prior therapies and whose disease is refractory to at least two PIs, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody* • **Selinexor/dexamethasone**
Useful in Certain Circumstances
After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD • **Belantamab mafodotin-blmf (if available through compassionate use program)**

CD = cluster of differentiation.

But what we're most interested in is currently the late line of therapy. For patients who have had 4 or more lines, we really have a few groups of options. One group is some of the novel agents like Selinexor, or belantamab. At the time of this recording, belantamab had been taken off the FDA market given the negative results of the DREAMM 3 study. However, the DREAMM 7 and DREAMM 8 studies are positive. So we're likely to see that drug come back into the fray. Otherwise a lot of our therapies include classical chemo, drugs like bendamustine and cyclophosphamide, but really what we're looking towards now in later relapses is utilizing T-cell redirection therapy. And as you can see at the top we have listed our CAR Ts and bispecific antibodies.

So let's talk about what happens as we go through this course.

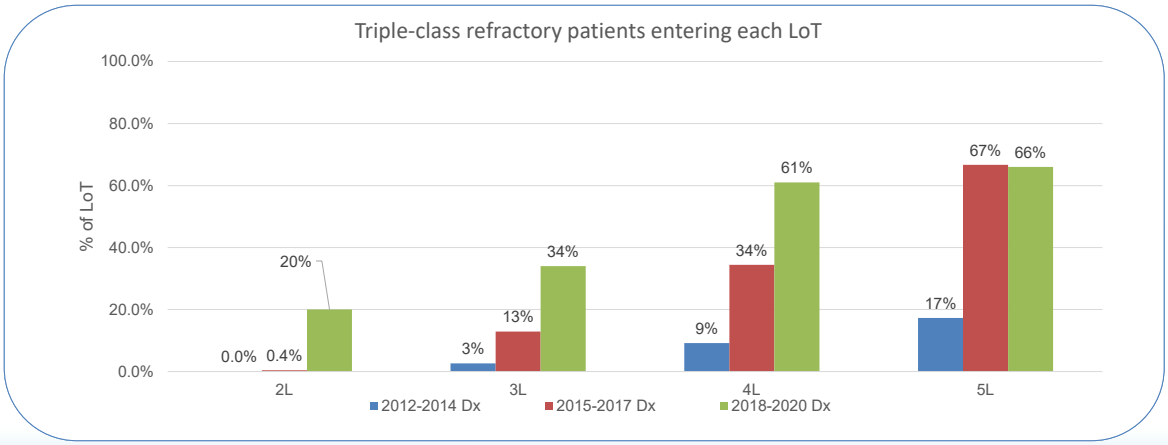
Once Treatment Fails, Trouble Begins



Kumar SK, et al. *Mayo Clin Proc*. 2004;79(7):867-874. Kumar SK, et al. *Leukemia*. 2012;26(1):149-157.

Essentially as you go from relapse 1, to relapse 2, to relapse 3, we recognize that the likelihood of getting a deep and durable remission goes down and patients become more and more refractory. Although one thing that is starting to change this is that our T cell redirection therapies are so efficacious. We have patients who have had 19 lines of therapy and then get one of these and that can be much more durable.

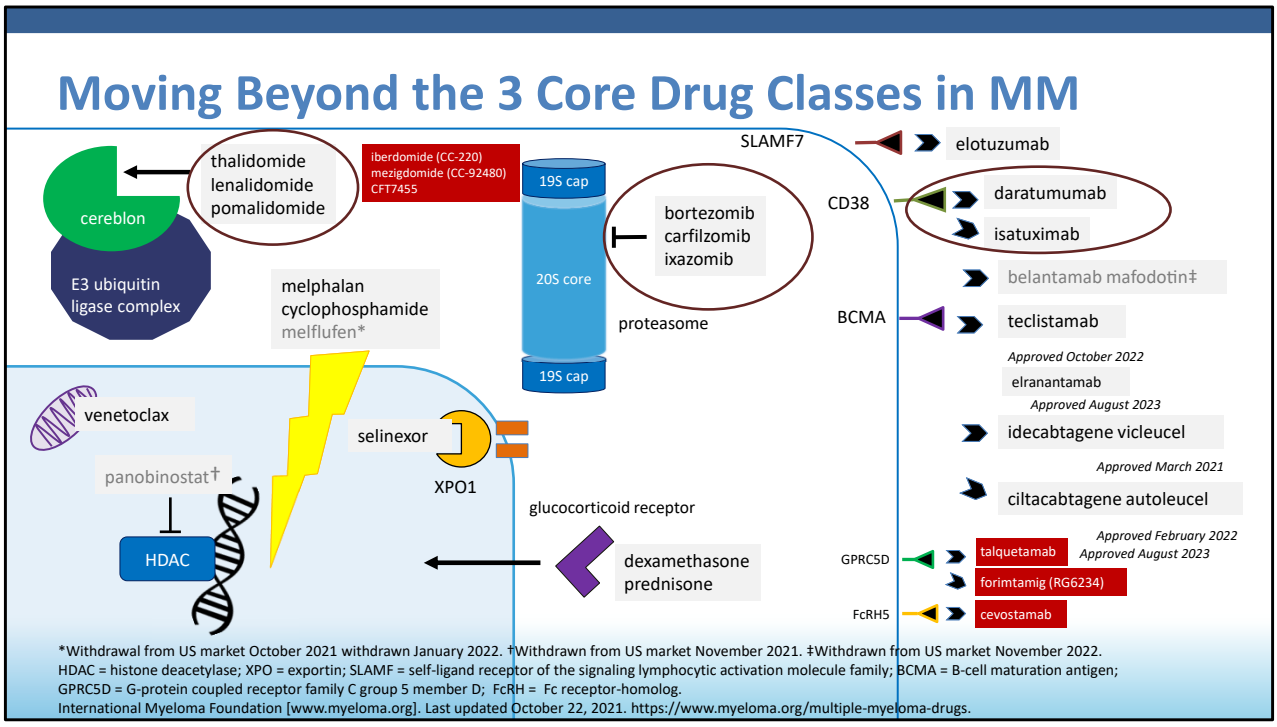
Triple-Class Refractory Patients Are Growing Quickly and Occurring Earlier in RRMM



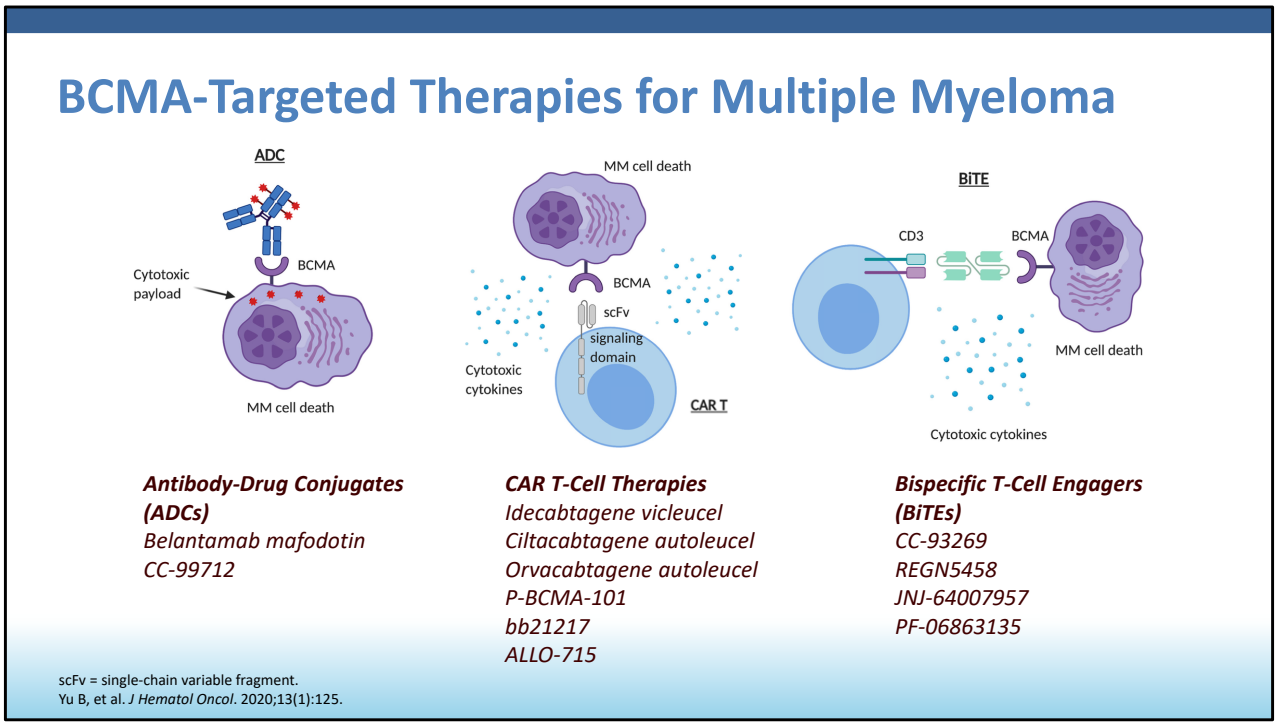
LoT = lines of therapy; Dx = diagnosis.
Company market research and analysis, Q2 2020. IQVIA patient data, 2015-2018.

But we recognize that the classic 3 types of treatments we've been using in the last decade, the IMiDs, the proteasome Inhibitors, and the monoclonal antibodies, we're using them in more and more combinations earlier on. So I remember a time where these were given in what we call sequential doublets, lenalidomide and dexamethasone, then pomalidomide and dexamethasone, then bortezomib and dexamethasone, carfilzomib dexamethasone, and dara and dexamethasone. It would take 5 lines of therapy to be what we call triple class refractory. Refractory to an immunomodulatory drug, like lenalidomide, a proteasome inhibitor like bortezomib, and a monoclonal antibody like daratumumab. But nowadays we're using regimens like Dara RVD up front. And if you progress on that, you can be triple class refractory going into your second line.

The Role of the ED in Treating Multiple Myeloma in the Era of Novel Immunotherapies



So we really need to go beyond those 3 core classes of drugs, the IMiDs, the proteasome inhibitors, and the monoclonals. I know this is a lot of setup, but really what this is taking us to is we're seeing some of the best response rates even in heavily refractory patients with the drugs on the right. The drugs that target T cells for activation either through engaging with one of the targets like BCMA or GPRC5D or fcRH5.

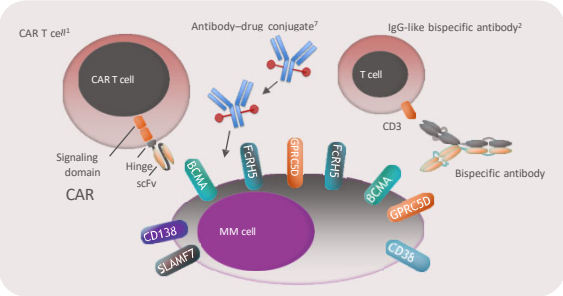


So let's start off with BCMA, because BCMA, also known as B cell maturation antigen, has become one of the most key targets of T cell redirection therapy. BCMA is widely expressed on plasma cells, specifically malignant plasma cells. Just like you may be familiar with the other CDs like retuximab, an anti-CD20 antibody, and daratumumab an anti-CD38 antibody, BCMA is CD269. Now we cannot use naked antibodies here like we can with other targets. We have to use some other technology, either an antibody drug conjugate like belantamab mafodotin, where the naked antibody has a warhead, the naked antibody engages with any BCMA expressing tumor cell, and then injects the poison.

Think about it like classical chemo, but instead of a systemic infusion, it's directly delivered to the malignant cell. Again, we only have one of these drugs that's currently off the market. Hopefully it will come back in the near future. But the two main ways we've been exploiting BCMA is either through the use of CAR T-cell therapies and we have a number of them under investigation, or through bispecific antibodies. Bispecific antibodies utilize a two arm structure, where one arm grabs onto the BCMA expressing malignant cell, the other arm grabs onto the CD3 expressing T-cell and activates the T-cell to attack the myeloma cell.

The Role of the ED in Treating Multiple Myeloma in the Era of Novel Immunotherapies

BsAbs→New-Generation Immunotherapies in MM



BCMA:
- Selectively overexpressed in plasma cells
- Promotes proliferation and survival of MM cells

GPRC5D:
- Highly and selectively expressed in MM
- Distribution is similar to but independent of BCMA

FCRH5:
- High levels of expression on MM cells
- Normally expressed in plasma cells only

- ADC:
  Belantamab
  MEDI2228
- Bispecifics:
  AMG701
  Teclistamab,
  talquetamab
  Elranatamab
  REGN5458
  TNB-383B
  CC-93269
  Cevostamab
- CAR T:
  Ide-cel
  Cilta-cel p-BCMA- 101
  CT053
  ALLO-715

Cilta-cel = ciltacabtagene autoleucel; FcRH5 = Fc receptor-like 5; ide-cel = idecabtagene vicleucel; Ig = immunoglobulin.
Rodríguez-Lobato LG, et al. *Front Oncol*. 2020;10:1243. Pillarisetti K, et al. *Blood Adv*. 2020;4(18):4538-4549. Yu B, et al. *J Hematol Oncol*. 2020;13(1):125. Verkleij CPM, et al. *Blood Adv.* 2020;5(8):2196-2215. Smith EL, et al. *Sci Transl Med*. 2019;11(485):eaau7746. Li J, et al. *Cancer Cell*. 2017;31(3):383-395. Bruins WSC, et al. *Front Immunol*. 2020;11:1155.
Images adapted from Verkleij CPM, et al. *Curr Opin Oncol*. 2020;32(6):664-671. Bruins WSC, et al. *Front Immunol*. 2020;11:1155.

With bispecific antibodies, we've gone beyond just utilizing BCMA as a target, although we have 2 currently approved BCMA bispecific antibodies, elranatamab and teclistamab. In the bispecific world we moved on to additional targets such as GPRC5D, another target that is ubiquitously expressed on plasma cells, specifically malignant plasma cells. Right now, we have the FDA approved bispecific talquetamab, with another bispecific, forimtamig under active investigation. And FCRH5, another target that's expressed widely, and independently on myeloma cells, and this is under investigation with the bispecific antibody cevostamab.

The Role of the ED in Treating Multiple Myeloma in the Era of Novel Immunotherapies

Bispecific Antibody	Alnuctamab (CC-93269)	Erlantamab	Linvoseltamab	Teclistamab	TNB-383B	Anti-GPRC5d Talquetamab	Anti-FcRH5 Cevostamab
Treatment	SC D1,4,8,15,22 C1, QW C2-3, Q2W C4-6, Q4W C7-beyond.	Weekly SC	Weekly IV	Weekly SC	IV q3w	SC	IV q3w
Patients	n=47	n=55	n=252 (Ph1 = 73; Ph2 = 179)	n=165	n= 60 (≥ 40 mg)	n=143 (0.4m/kg qwk), n=145 (0.8 mg/kg q2wk)	n=160
Median prior lines	4	5	5	5	5	6/5	6
Triple-class refractory	62%	91%; 24% prior BCMA-directed	81%	78%	65%	74%/69%	85%
ORR @	10/13 (77%)	64%	64%	63%	79% (n=24 mature)	74%/73%	55% (160 mg) 37% (90mg)
therapeutic dose	≥ 30 mg SC	215-1000 µg/kg SC	200 mg cohort (n=58)	1.5 mg/kg SC	≥ 40 mg		15.6 months
Duration of response	NR	17.1 m	NR	18.4 months			
AEs, (All %/(Gr 3+%)	89% (62%)		95% (66%)	100% (95%)	77% (32%)	79%/75%	99% (59%)
CRS	53% (0%)	67% (0%)	37% (1%)	72% (1%)	52% (3%)	58%/65%	80% (1.3%)
Infections				76% (45%)	28%		43% (19%)
Neutropenia	34% (30%)			71% (64%)	17%	ICANS 11%-11%	18% (16%)
Anemia	34% (17%)		28% (24%)	52% (37%)		Skin-related AEs 56%-71%	32% (22%)
Thrombocytopenia				40% (21%)		Nail-related AEs 54%-53%	Deaths 1pt (0.6%)
Deaths (n/%)					Deaths 5 (5%)	Dysgeusia 50%-48%	Neurological/ Psychiatric 41% (4%)
Other		ICANS 0% (0%)	ICANS 2% (2%)	Neurotox 15% (1%) ICANS 3 (0%)			

SC = subcutaneous; IV = intravenous; q = every; w = week(s); ORR = overall response rate.

Wong SW, et al. *Blood*. 2022;140(Suppl 1):400-402. Raje N, et al. Presented at the 64th American Society of Hematology (ASH) Annual Meeting; December 10, 2022; New Orleans, Louisiana. Lee HC, et al. *J Clin Oncol*. 2023;41(16_suppl):8006. Moreau P, et al. *N Engl J Med*. 2022;387(6):495-505. Kumar S, et al. *Blood*. 2021;138(Suppl 1):900. Schinke CD, et al. *J Clin Oncol*. 2023;41(16_suppl):8036. Trudel S, et al. Blood. 2021:138(Suppl 1):157.

But ultimately when we're talking about bispecific antibodies, we group them into the BCMA types and the non-BCMA types. Now just to put this into context of how great some of these drugs are, if you look across the last 10 to 15 years of FDA approvals for myeloma. In general, when a new drug comes to market that's given at the end of the line, either by itself or with a little bit of steroid, the response rates have varied between 22 and 30% and have achieved FDA approval. So pomalidomide, carfilzomib, daratumumab, belantamab, or even selinexor, all of these drugs that have been approved with response rates between 22 and 30%, and a progression-free survival around 6 months, all approved by the FDA.

Now if you look at all the BCMA bispecifics, you'll see response rates ranging between 60 and 80% with progression-free survivals in some of these trials of well over a year, and some even quite a bit longer.

Again, at the time of this recording, if we look at the top elranatamab and teclistamab are FDA approved. Linvoseltamab has had its BLA accepted by the European Medical Association and the FDA, currently under review hoping for approval later this year. When it comes to the non-BCMA bispecifics, talquetamab and cevostamab on the right. Again, we're seeing response rates of between 60 and 80%, very durable. But again, these are coming with them a whole new set of toxicities.

BCMA-Bispecific mAbs: Safety Profile

	AMG-701[1]	CC-93269[2]	Teclistamab[3]	Elranatamab[4]	REGN5458[5]	TNB383B[6]
CRS (G 3-4) Median onset Duration Tocilizumab	64% (9%) - - 29%	76.7% (3.3%) 1 (1-9) 2 (1-6) 43%	71.5% (0.6%) 2(1-6) 2(1-9) 36.4%	60.6% (0%) 3 4(1-10) 50%	38% (0%) 10.1(6-47) hours 14 (0-96) hours 43%	69% (4%) 1(1-2) 1(1-8)
NTS Grade 3-4 ICANs Median onset Duration Treatment required	Not reported	Not reported	15% 0.6% 3% 2.5(1-7) 3(1-37) 7.3%	6.4% 1.1% 0% NR NR NR	0% 4% (g2)	0%
Cytopenias Grade 3-4 Neutropenia Anemia Thrombopenia	 25% 42% 21%	 37% 43% 17%	 57% 34,5% 21.2%	 67.3% 47.3% 27.3%	 22% 23% 13%	 24% 15% 9%
Infections Grade 3-4	 17%	 30%	63% 35%		5 exitus infecc	 28%
Hypogammaglobulinemia as AEs observed in most patients treated with BCMA-CD3 mABs along the therapy.						

NTS = neurotoxic syndrome; mAb = monoclonal antibody.
Harrison SJ, et al. Presented at the 62nd ASH Annual Meeting; December 5-8, 2020. Abstract 181. Costa LJ, et al. Presented at the European Hematology Association (EHA) 2020 Congress; June 11-21, 2020; virtual. Abstract S205. Moreau P, et al. Presented at the 63rd ASH Annual Meeting; December 11-14, 2021; Atlanta, Georgia. Abstract 896. Sebag M, et al. Presented at the 63rd ASH Annual Meeting; December 11-14, 2021; Atlanta, Georgia. Abstract 895. Zonder JA, et al. Presented at the 63rd ASH Annual Meeting; December 11-14, 2021; Atlanta, Georgia. Abstract 160. Kumar SK, et al. Presented at the 63rd ASH Annual Meeting; December 11-14, 2021; Atlanta, Georgia. Abstract 900.

So really, the meat of this is really talking about what are the new adverse events that we see with these types of therapies? Now in my mind, there are early toxicities and late toxicities. The early ones are adverse events that tend to occur during the step-up period. So for bispecific antibodies as opposed to CAR Ts, where CAR Ts we give the entire dose, cellular dose at one time, for bispecifics instead of giving the full dose we ramp it up slowly so that we don't overwhelm the immune system. Because the immune system we always want, like Goldilocks, we don't want it too cold where it's not fighting the myeloma. We don't want it too hot where it's going haywire. We want it in the Goldilocks zone. When it gets over activated, that's what we call CRS, or cytokine release syndrome, and it can even lead to things like ICANS the immune effector cell-associated neurotoxicity syndrome.

These adverse events tend to occur early on during that initial step up period which usually lasts around a week. You can get some lower blood counts during this time. So cytopenias are common. However, the use of white cell growth factors, like filgrastim, Neupogen, Granix can actually exacerbate the risk of CRS early on. So if you're concerned about CRS and the patient presents to the emergency room and they're neutropenic, you may want to hesitate before giving GCFS so that you don't exacerbate this. Infections can occur early on, but a lot of this occurs a little bit later on, once the drug has had a chance to deplete a lot of the immune producing cells.

Anti-GPRC5D Bispecific Antibodies


Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D × CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma: Phase 1/2 Results From MonumenTAL-1


Forimtamig (RG6234), a GPRC5DxCD3 T-cell-engaging bispecific antibody, is highly active in patients with relapsed/refractory multiple myeloma: updated intravenous and first subcutaneous results from a Phase I dose-escalation study

GPRC5D

- G protein-coupled receptor class C group 5 member D
- Orphan receptor of unknown function
- High expression in myeloma cells; some expression in normal plasma cells; expression independent of BCMA
- Limited expression in normal tissues; **but expression in hair follicles, central region of tongue**
- Not shed (unlike soluble BCMA), reduced risk for sink effect
- Not in memory B cells or progenitor cells

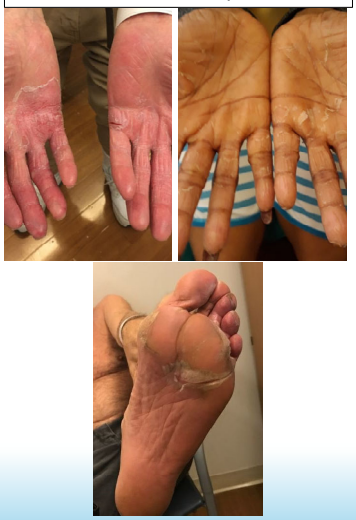
	N	Prior BCMA	ORR | ≥VGPR	PFS	CRS (all | ≥3)	Tociliz.	Schedule	Comments
Talquetamab Chari A et al., ASH 2022	145†	11% (bela)	73.1% | 57.2%	11.9 months	72.4% | 0.7%	36.6%	sc q2 weeks	0.8 mg/kg sc q2 weeks Grade 3-4 infections, 11.7% **Any grade skin 67.6%; nail 43.4%; dysgeusia 46.2%**
Forimtamig* (RG6234) Carlo-Stella C et al. ASH 2022	57*	21.1%	63.6% | 52.8%		78.% | 1.8%	25.9%	sc q2 weeks	1200-7200 µg q2 weeks Grade 3-4 infections, 26.4% Any grade skin 86%, nail 28.1%

*91.2% triple class exposed. †Separate cohort (weekly N=43; q2 week N=8) with ORR 72.2% with prior CAR T-cell therapy (out of N=36) and 44.4% prior bispecific antibody (out of N=18). Chari A, et al. Presented at the 64th ASH Annual Meeting; December 10-13, 2022; New Orleans, Louisiana. Carmelo CS, et al. Presented at the 64th ASH Annual Meeting; December 10-13, 2022; New Orleans, Louisiana.

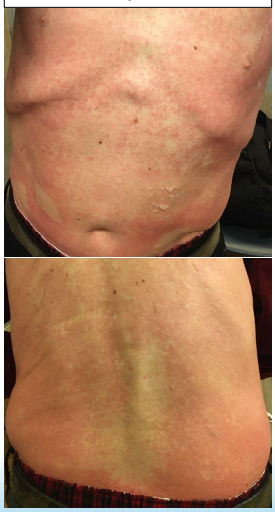
So when it comes to the GPRC5D bispecific antibodies, there are talquetamab and forimtamig. One of the things that's really important to note is that the GPRC5D as a target is very different from BCMA. So BCMA that we've talked a little bit about CD269, is really only expressed on immune-related cells, specifically plasma cells and a little bit on B cells, as well. There's not a lot of off-target expression. GPRC5D is located more on malignant plasma cells. It's actually less expressed on B cells. It's not really even expressed on B cells, but it's located on the squamous epithelium of the hands and feet and people can get a desquamating rash that kind of reminds me of Xeloda. So you get this desquamating, peeling rash. It's also located on the oral pharynx and salivary gland. So people can get dry mouth, dysgeusia and even trouble swallowing, anorexia, and weight loss. So it can be a little more difficult to tolerate.

Non-Hematologic Toxicities of Talquetamab

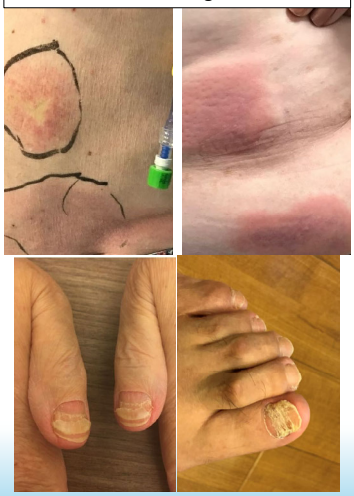
Palmar/Plantar Desquamation



Body Rash

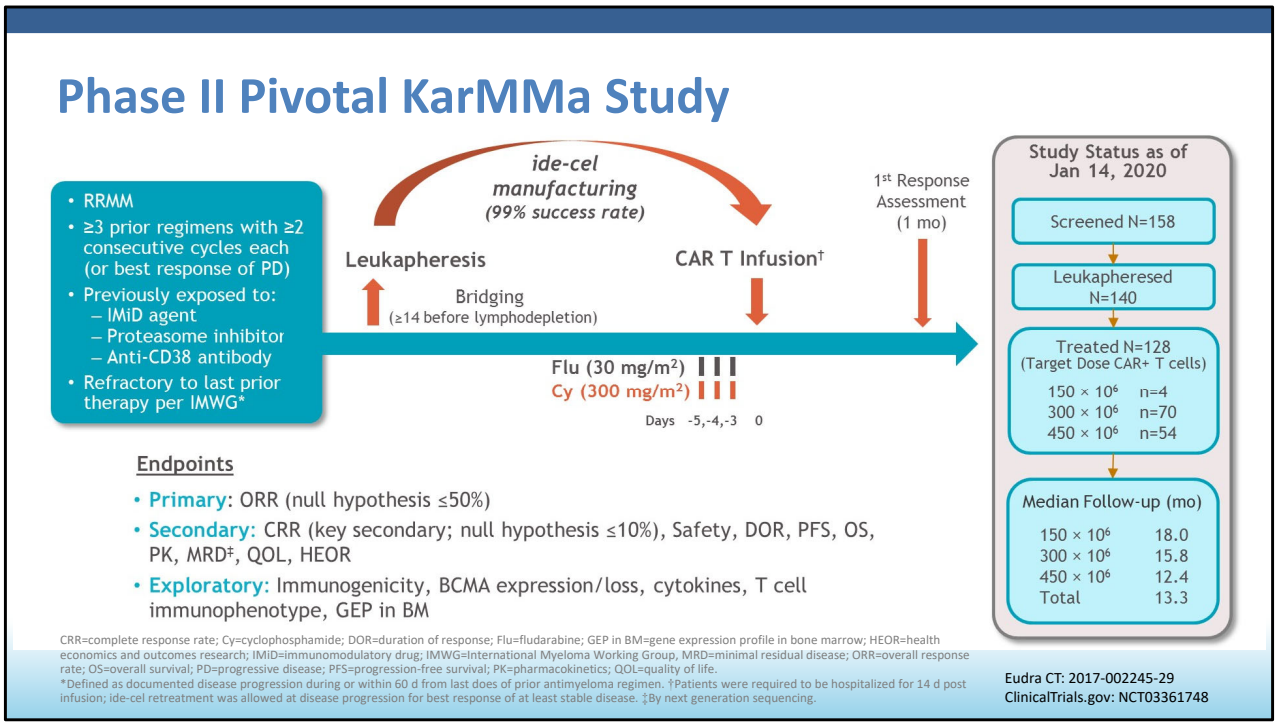


Injection Site Reactions/ Nail Changes



Ray, et al. Presented at the 20th International Myeloma Society Annual Meeting; September 27-30, 2023; Athens, Greece.

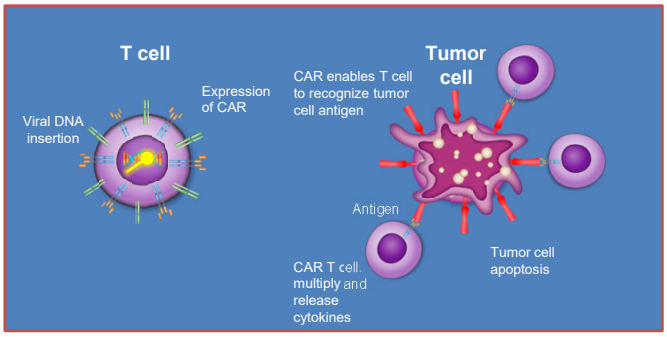
Here are some of the non-hematologic toxicities of talquetamab. Again on the right you can see the injection site reactions. But really what we see is, thinning of the nails, diffuse maculopapular body rashes, and this desquamating palmar/plantar rash that we can see on the left on the hands and feet.



When it comes to CAR T, this is kind of the mainstay of what we talk about when we're talking about immunotherapy. Essentially this really comes from the concept of the best cancer fighter is our own immune system. Although bispecifics are off the shelf, they're really just using the T cells laying around. The goal here is first we pheresis, or collect the T cells of a patient. And then in the lab, we engineer them and expand them. So now we have a huge group of T cells that are all targeting BCMA. So it's like taking some first day Army recruits, sending them off to special training, you know getting a whole bunch of them together and then giving them bazookas and sending them back in the fight. That manufacturing process can take up to 4 to 8 weeks at the current time. There are ongoing studies to shrink that.

During that time we want to make sure that the patient's disease doesn't cause them any trouble. So we typically give them what we call bridging therapy. Basically, chemotherapy designed to hold the myeloma at bay while we manufacture the CAR T product. When it's ready to go, we can't just infuse that product because right now we all have T cell repertoires. T cells to fight bacteria, viruses, a whole variety of diseases. If we only infuse that CAR T, now it's just a voice amongst the crowd. We need to create immunologic space. We do this by first giving what we call lympho-depleting chemotherapy, three days of a combination of fludarabine and cyclophosphamide, neither of which is designed to kill the myeloma, but basically to turn the patient into an AIDS patient and eradicate their endogenous T-cells so that when we inject the CAR T it is the dominant T cell force in their body.

How CAR T-Cell Therapy Works



DNA = deoxyribonucleic acid.

How this works–we take a T-cell, use viral DNA to insert this and express, and basically target that BCMA. When they get infused, they latch on to the tumor cells, and they release granzymes and perforins to kill the tumor cells. Essentially this is how CAR T works.

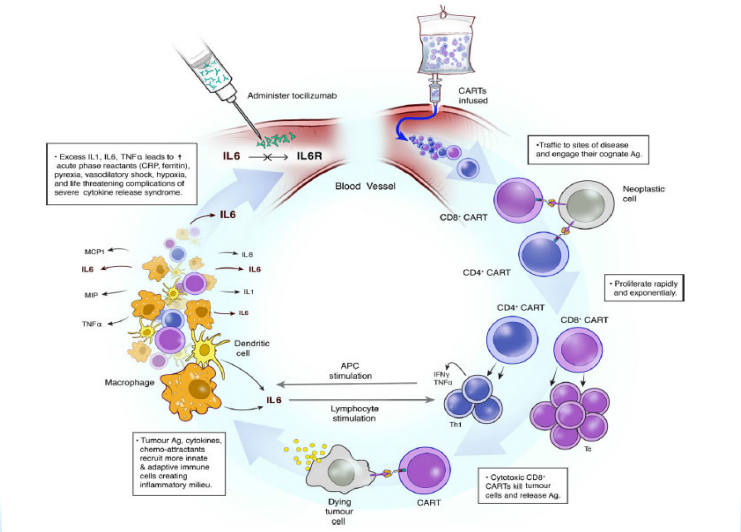
CAR T-Cells in Myeloma

	Approved CAR T-cells		Academic	Alternative manufacturing	Human scFv		Allo-CAR	GPRC5D
	Ide-cel KarMMa (n=128)	Cilta-cel CARTITUDE-1 (n=97)	ARI0002h (n=30)	P-BCMA-101 PRIME (n=53)	CT053 LUMMICAR (n=24)	CT103A (n=79)	ALLO-715 UNIVERSAL (n=43)	MCARH10 (n=17)
Phase	II	Ib/II	I/II	I/II	I	I/II	I	I
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	GPRC5D
scFv	Chimeric mouse	Chimeric llama	Humanized	Chimeric mouse	Human	Human	Human	Human
Co-stim	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB
Specificity	Autologous	Autologous	Autologous	Autologous - piggyBac	Autologous	Autologous	Allogenic CD52 & TCR KO	Autologous
Age, (range)	61 (33-78)	61 (56-68)	61 (36-74)	60 (42-74)	62 (33-76)	57 (39-70)	64 (46-77)	60 (38-76)
# of lines	6	6	4	8	NA	5	5	6
HR cytog, %	35	24	33	NA	NA	34	37	77
EMD, %	39	13	20	NA	NA	13	21	41
Triple-R, %	84	88	67	60	NA	17	91	94
ORR, %	81	98	100	67	87	95	71	69
CR/sCR, %	39	82	63	NA	NA	68	25	25
PFS	12.2 m	55%@27 m	53%@18 m	NR	NR	NR	NR	NR

*There are no head-to-head comparisons of these data, and naïve comparison should be conducted with caution.
BCMA = B-cell maturation antigen; EMD = extramedullary disease; HR cytog = high-risk cytogenetics; NA = not available; NR = not reached/not reported; ScFv = single-chain variable fragment; TCR = T-cell receptor; triple-R = triple-class refractory; PFS = progression-free survival.
Anderson L, et al. Presented at ASCO Annual Meeting; June 4-8, 2021; Chicago, Illinois. Abstract 8016. Berdeja J, et al. *Lancet*. 2021;398(10297):314-324. Lin Y, et al. Presented at the EHA2022 Congress; June 9-17, 2022; Vienna, Austria. Abstract P961. Fernández de Larrea C, et al. Presented at the EHA2022 Congress; June 9-17, 2022; Vienna, Austria. Abstract S103. Costello C, et al. Presented at 62nd ASH Annual Meeting; December 5-8, 2020; virtual. Abstract 134. Mohyuddin GR, et al. *Blood Adv*. 2021;5(4):1097-1101. Li C, et al. Presented at the EHA2022 Congress; June 9-17, 2022; Vienna, Austria. Abstract S187. Li C, et al. Presented at the 63rd ASH Annual Meeting; December 11-14, 2021; Atlanta, Georgia. Abstract 143. Mailankody S, et al. Presented at the 63rd ASH Annual Meeting; December 11-14, 2021; Atlanta, Georgia. Abstract 651. Mailankody S, et al. Presented at the 63rd ASH Annual Meeting; December 11-14, 2021; Atlanta, Georgia. Abstract 827.

Now we have a bunch of them in clinical trial. The two on the left are the currently approved ones, ide-cel and cilta-cel. But there are ongoing studies to look at developing them at academic centers, rapid manufacturing, dual targeting, alternative targeting, and even Allo-CARs, off the shelf allogeneic CAR Ts, that won't need to be manufactured at the time from the patients themselves. So, you don't have to worry about that manufacturing time, but you still have to kind of worry a little bit about graft versus host disease.

Biological Consequences Following Car T-Cell Infusion



IL = interleukin; TNF = tumor necrosis factor; CRP = C-reactive protein; Ag = antigen; MIP = macrophage inflammatory protein; APC = antigen-presenting cells.
Orlowski RJ, et al. *Br J Haematol*. 2017;177(1):13-26.

So what happens when we infuse those CAR Ts into you? Essentially we infuse the CAR T-cells, the T-cells expand, they engage with tumor cells, and one of the biggest things that we get is not only T-cell activation and T-cell expansion, but we get broad-based immune responses with heavy release of a variety of chemokines and cytokines, specifically things like interleukin-1, interleukin-6, TNF alpha, TGF beta, and we can get a variety of sequelae from it.

Infection and Death in Patients Refractory to Lenalidomide

Rates of infection, grade 3 or higher infection, and deaths from infection across selected relapsed/refractory multiple myeloma trials enrolling patients refractory to lenalidomide

Regimen	Timing of last enrolled patient	Median lines of prior therapy (range)	Overall infection rate (%)	Grade ≥ 3 infection rate (%)	Grade ≥ 3 COVID-19 rate (%)	Deaths from infections /COVID (%)	Median follow-up (months)	Median duration of therapy (months)
Dara-Pd [7]	Pre-COVID	1 (1–5)	71	30	N/A	5	16.9	11.5
Dara-Kd [8]	Pre-COVID*	1 (1–2)	NR	47	< 1	5	27.8	18.3
Teclistamab [2]	COVID era	5 (2–14)	76	45	12.1	12/7	14.1	8.5
Talquetamab [1]^	COVID era	6 (2–17)	47	7	3	0/0	11.7	NR
ABBV-383 [9]	COVID era	5 (3–15)	41	25	6	36/2.5	10.8	NR
Idecabtagene vicleucel [5]	Pre-COVID* and COVID era	3 (2–4)	58–70	26–28	NR	3–5/0.8	13.3–18.6	N/A
Ciltacabtagene autoleucel [10]	Pre-COVID*	6 (4–8)	59	28	N/A	5/0	28	N/A

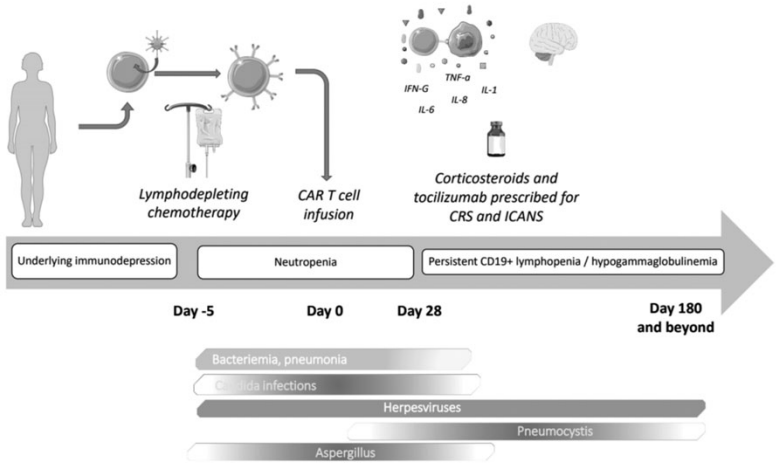
Abbreviations: N/A = not applicable; NR = not reported; COVID: Coronavirus Disease.
*Follow-up included time during COVID era (March 2020 onwards).
^Sufficient follow-up only reported at 405 µg dose.

20th IMS Annual Meeting; September 27-30, 2023; Athens, Greece. Rubinstein SM, et al. *Eur J Cancer*. 2023;189:112926.

Now one of the things to note is that when we undergo either bispecific antibodies or CAR T cells, we are inducing a broad range of immune suppression. This is multifactorial, so number 1 we're giving drugs that kill immune producing cells. So we kill some bad plasma cells while we kill some good ones and often time some good lymphocytes. So we lose part of our humoral immunity and ability to produce antibodies or what we call hypogammaglobulinemia. In addition, we also have cytopenias, and neutropenia is not uncommon in this.

The other one is a little weird to think of, but T cell redirection means you have T cells that were designed to fight bacteria, viruses, and cancer and you're either eradicating them with a CAR T and then giving another t-cell back that CAR T, or in bispecific antibodies you're grabbing them and saying don't fight the bacteria and the viruse. Come here to fight the cancer, in which case nobody's minding the shop. Infection wise, we see some of the highest rates of infection we've ever seen with drugs like teclistamab, showing an overall infection rate of around 76% with almost half of those infections being grade 3 or higher.

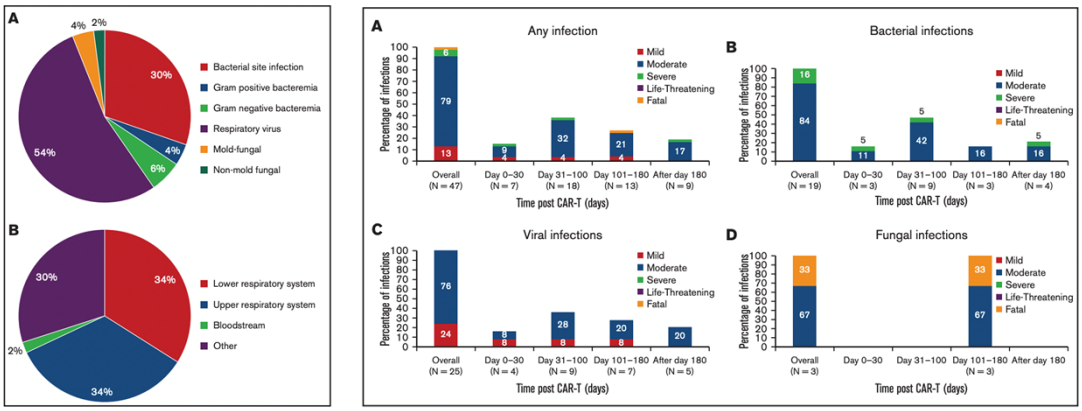
CAR-T Therapy and Multifaceted SID



Joseph, et al. *Curr Opin Crit Care*. 2022 Oct 1;28(5):540-550.

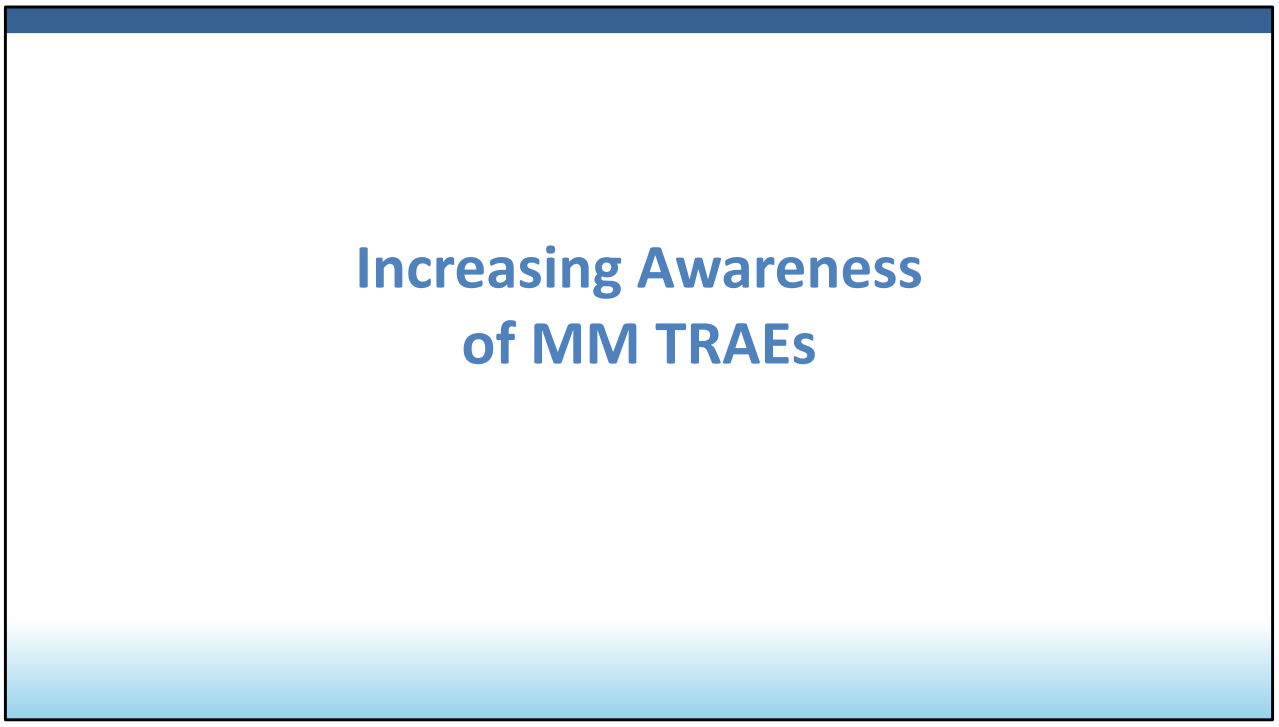
The way we overcome this is mostly through the use of both antibiotic and antiviral prophylaxis, but judicious use of IVIG intravenous immunoglobulin. With CAR T the immune dysfunction is still multifaceted, or you get a combination of cytopenias, and humoral deficiency from the lymphodepletion. But the neutropenia and the immunosuppression can last for quite a bit of time. Initially during that step-up period, or during the initial post infusion CAR T period, we're seeing mostly bacterial infections, oral candidiasis, but as we go on we tend to see a little more viral, and even PJP reactivation.

Infection Patterns Post CAR-T in Myeloma



Kambhampati, et al. Blood Adv. 2022 Apr 12;6(7):2045-2054.

When it comes to patients with infection patterns, again, the majority of infections we're going to see post CAR T. So if someone comes in with a fever and they've had a prior CAR T therapy, again really depends upon where they're coming in, you know, 1 week out, 1 month out, 6 months out, but most of the infections are upper respiratory, and some lower respiratory, but respiratory infections, remembering that the very large amount of immune cell burden is located within the pulmonary vasculature. So when we wipe that out, we really put patients at risk for URIs, and we can see that here. We do see a variety of viral reactivation. So patients who do have fevers that are far out, we do worry about things like CMV and EBV reactivation and given the fact that, remember I mentioned we're giving lymphodepletion chemotherapy to essentially wipe out T cells and turn these patients into AIDS patients. We're seeing rises in pneumocystis pneumonia. So our general schema is to provide pneumocystis prophylaxis until the CD4 count goes back up above 200. If you do see a patient in the ER with a PJP like pattern, an LDH rising, it's worthwhile to think about PJP pneumonia.



The big thing we want to focus on is raising awareness of the immune-related adverse events.

NCCN Guidelines: Management of Immunotherapy-Related Toxicities

OVERVIEW OF CAR T-CELL THERAPY-RELATED TOXICITIES

	Axicabtagene Ciloleucel, Brexucabtagene Autoleucel, Idecabtagene Vicleucel, Lisocabtagene Maraleucel, and Tisagenlecleucel[a]
CRS (CART-3)	• Typical time to onset: 2–3 days; however, CRS may occur as early as hours after infusion and as late as 10-15 days post-infusion • Typical duration: 7–8 days • Manifestation may include fever, hypotension, tachycardia, hypoxia, and chills. CRS may be associated with cardiac, hepatic, and/or renal dysfunction. • Serious events may include hypotension, hypoxia, atrial fibrillation and ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).[b]
Neurologic Toxicity (CART-4)	• Typical time to onset: 4–10 days • Typical duration: 14–17 days • Transient neurological symptoms can be heterogeneous and include encephalopathy, delirium, aphasia, lethargy, headache, tremor, myoclonus, dizziness, motor dysfunction, ataxia, sleep disorder (eg, insomnia), anxiety, agitation and signs of psychosis. • Serious events including seizures, depressed level of consciousness, as well as fatal and serious cases of cerebral edema, have occurred.
Hemophagocytic Lymphohistiocytosis/ Macrophage-Activation Syndrome (HLH/MAS) (CART-3)	• Criteria for considering HLH/MAS: ▯ Rapidly rising and high ferritin (>5000 ng/mL) with cytopenias in the context of fever, especially if accompanied by *any of the following*: ◊ Grade ≥ 3 increase in serum bilirubin, AST, ALT ◊ Grade ≥ 3 oliguria or increase in serum creatinine ◊ Grade ≥ 3 pulmonary edema ▯ Presence of hemophagocytosis in bone marrow or organs based on histopathologic assessment of cell morphology and/or CD68 IHC.
Miscellaneous	• Patients may exhibit cytopenias for weeks to months following lymphodepleting chemotherapy and CAR T-cell therapy infusion. • Long-term B-cell aplasia and hypogammaglobulinemia can occur in patients with a complete remission after CAR T-cell therapy infusion. ▯ After anti-CD19 CAR T-cell therapy, consider monthly 400–500 mg/kg IVIG replacement for select patients with hypogammaglobulinemia (those with serum IgG levels <400–600 mg/dL AND serious or recurrent infections [particularly bacterial]). Continue IVIG until serum IgG levels normalize and infections resolve. The optimal IgG threshold to use may depend on patient characteristics and infection frequency/severity.

Thompson JA, et al. *J Natl Compr Canc Netw*. 2022;20(4):387-405.

Again we talked about the main ones, CRS and ICANS, there's a few others including HLH, which we'll talk about. One of the things that when we talk about CRS and ICANS is that you can have CRS without ICANS, you can have ICANS without CRS, or what is the more common pathway is that CRS comes on, and then ICANS if it's going to show up, follows. Oftentimes we're able to treat the CRS before we ever get ICANs. So CRS is far more common, but how they occur, and if they occur independently of one another helps dictate how we manage this in the clinic, or in the emergency room.

Cytokine Release Syndrome

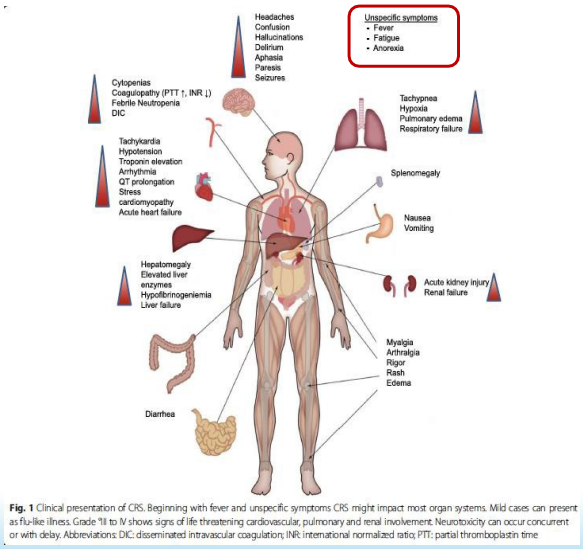


Fig. 1 Clinical presentation of CRS. Beginning with fever and unspecific symptoms CRS might impact most organ systems. Mild cases can present as flu-like illness. Grade °II to IV shows signs of life threatening cardiovascular, pulmonary and renal involvement. Neurotoxicity can occur concurrent or with delay. Abbreviations: DIC: disseminated intravascular coagulation; INR: international normalized ratio; PTT: partial thromboplastin time

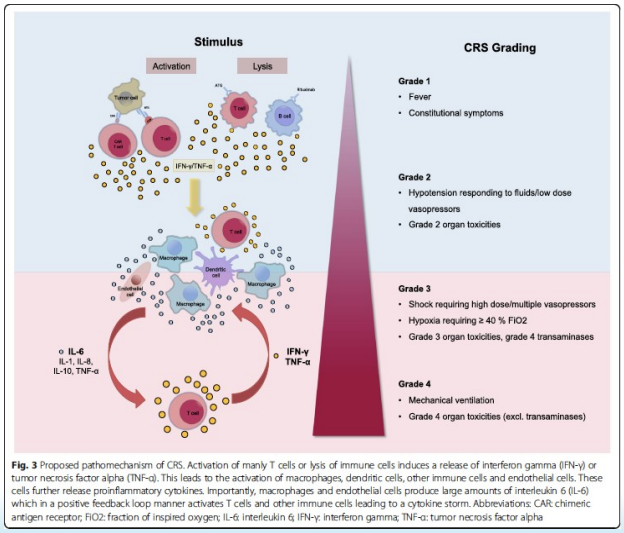


Fig. 3 Proposed pathomechanism of CRS. Activation of manly T cells or lysis of immune cells induces a release of interferon gamma (IFN-γ) or tumor necrosis factor alpha (TNF-α). This leads to the activation of macrophages, dendritic cells, other immune cells and endothelial cells. These cells further release proinflammatory cytokines. Importantly, macrophages and endothelial cells produce large amounts of interleukin 6 (IL-6) which in a positive feedback loop manner activates T cells and other immune cells leading to a cytokine storm. Abbreviations: CAR: chimeric antigen receptor; FIO2: fraction of inspired oxygen; IL-6: interleukin 6; IFN-γ: interferon gamma; TNF-α: tumor necrosis factor alpha

Shimabukuro-Vornhagen A, et al. *J Immunother Cancer*. 2018;6(1):56.

So cytokine release syndrome is simply this: it's a syndrome, a constellation of circumstances that leads to things like fever, hypoxia, tachycardia, hypotension. What does that sound like? Well that sounds to me a whole lot like sepsis, and one of the big ways that we help differentiate between the two is timing. If I give you a bispecific antibody in the morning and at noon you have fever, that is CRS. If I gave you a CAR T in January and in August, you have a fever, that is infection. It's the middle ground, a week into it, that's where you may not know if this is CRS, or infection and that's where sometimes you have to treat both at the same time.

One of the things if I leave you with anything is, I approach CRS and a lot of these scenarios in a similar vein to how we approach COPD, right? You have someone who presents to your ER with a COPD exacerbation, you oftentimes give them steroids and antibiotics. There is nothing wrong if you are unsure about where you are with this constellation of symptoms to give some steroid and antibiotics. Follow-up cultures the next day after they're admitted, and then adjust therapy as indicated. And again, we have a CRS grading that starts with things as limited as fever, but progress all the way to ICU requirement.

ASBMT CRS Grading

ASBMT CRS Consensus Grading[#]#

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever††	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With either:				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or‡‡				
Hypoxia	None	Requiring low-flow nasal cannula^ or blow-by	Requiring high-flow nasal cannula^, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

ASBMT = American Society for Blood and Marrow Transplantation; CRS = cytokine release syndrome; CPAP = continuous positive airway pressure; BiPAP = bilevel positive airway pressure.
Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

And again, we look at the ASBMT CRS grading. In many institutions we treat CRS only when it gets to grade 1, some institutions wait till grade 2, but we certainly want to prevent grade 3 or grade 4.

NCCN Guidelines: Cytokine Release Syndrome (CRS)

CRS Grade	Anti-IL-6 Therapy	Corticosteroids[j,k,l]	Additional Supportive Care
Grade 1 Fever (≥38°C)	For prolonged CRS (>3 days)[h] in patients or those with significant symptoms, comorbidities and/or are elderly, consider 1 dose of tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg)[i,†]	For idecabtagene and lisocabtagene, consider dexamethasone 10 mg IV every 24 hours for early-onset CRS (<72 hours after infusion)	• Sepsis screen and empiric broad-spectrum antibiotics, consider granulocyte colony-stimulating factor (G-CSF) if neutropenic[q] • Maintenance IV fluids for hydration • Symptomatic management of organ toxicities
Grade 2 Fever with hypotension not requiring vasopressors and/or hypoxia[f] requiring low-flow nasal cannula[g] or blow-by	Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose).[j] Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total[†]	For persistent refractory hypotension after 1–2 doses of anti-IL-6 therapy: Consider dexamethasone 10 mg IV every 12-24 hours depending on product[m,n]	• IV fluid bolus as needed • For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vasopressors, consider transfer to ICU, consider echocardiogram, and initiate other methods of hemodynamic monitoring. Telemetry, EKG, troponin, and BNP if persistent tachycardia • Manage per Grade 3 if no improvement within 24 hours after starting anti-IL-6 therapy • Symptomatic management of organ toxicities
Grade 3 Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula,[g] face mask, nonrebreather mask, or Venturi mask.	Anti-IL-6 therapy as per Grade 2[j] if maximum dose not reached within 24-hour period	Dexamethasone 10 mg IV every 6 hours.[m] If refractory, manage as grade 4	• Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring • Supplemental oxygen • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities
Grade 4 Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, mechanical ventilation).	Anti-IL-6 therapy as per Grade 2[j] if maximum dose not reached within 24-hour period	Dexamethasone 10 mg IV every 6 hours.[m] If refractory, consider 3 doses of methylprednisolone 1000 mg/day IV; if refractory, consider dosing every 12 hours[o,p]	• ICU care and hemodynamic monitoring • Mechanical ventilation as needed • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities

Thompson JA, et al. *J Natl Compr Canc Netw*. 2022;20(4):387-405.

How do we treat it? Well, if you have grade 1, either prolonged grade 1 or grade 2, we typically treat as a first line therapy with a drug called tocilizumab. Tocilizumab is an anti-IL-6 therapy. Another one is siltuximab, but tocilizumab or toci is usually our first go-around. Now, you may not have this in your emergency department. This drug is not always available. If you do not have this drug available and you think the patient may have CRS, we typically give steroids, most notably dexamethasone because of its potency, its half-life, and the penetrance into the CNS. The dose is 10 milligrams. Now in some cases we dose as frequently as 10 IV q6, but I think if someone had a bispecific antibody last week and presents to your ER with fever, tachycardia, and hypoxia, I see no problem with giving dexamethasone 10 milligrams IV, drawing cultures, giving antibiotics, and then reevaluating the patient's response. Again, you may want to avoid GCSF during the step-up period but if they're outside of the step-up period and you really don't think it's CRS you can consider giving it, but I would proceed with caution there.

ASCO Guidelines: Cytokine Release Syndrome

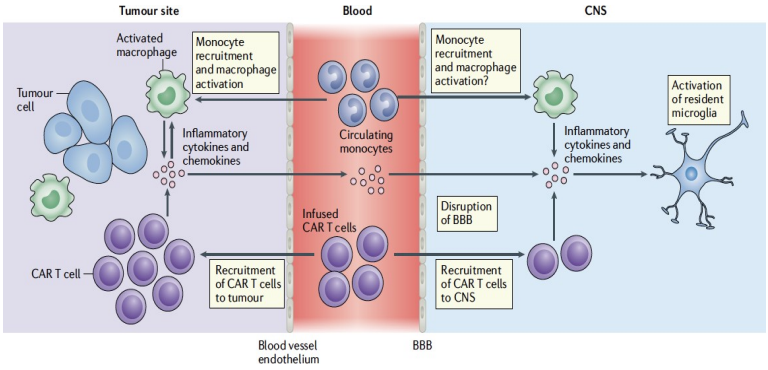
Workup or evaluation and supportive care recommendations (all grades):
- CBC, CMP, magnesium, phosphorus, CRP, LDH, uric acid, fibrinogen, PT/PTT, and ferritin
- Assess for infection with blood and urine cultures, and a chest radiograph if fever is present
- If patient is neutropenic, follow institutional neutropenic fever guidelines
- Patients who experience grade 2 or higher CRS (eg, hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function.
- Perform cardiac monitoring in patients who experience at least G2 CRS, clinically significant arrhythmia, and additionally as clinically indicated
- Consider screening for CMV and EBV
- Consider chest or abdominal CT imaging, brain MRI, and/or lumbar puncture.

Grading (on the basis of ASTCT consensus grading)[10]	Management
G1: Fever[a]: temperature ≥ 38°C not attributable to any other cause Hypotension: none Hypoxia: none	Offer supportive care with antipyretics, IV hydration, and symptomatic management of organ toxicities and constitutional symptoms May consider empiric broad-spectrum antibiotics if neutropenic. May consider G-CSF in accordance with product guidelines. Note: GM-CSF is not recommended In patients with persistent (> 3 days) or refractory fever, consider managing as per G2
G2: Fever[a]: temperature ≥ 38°C not attributable to any other cause *plus* Hypotension: not requiring vasopressors *And/or* Hypoxia: requiring low-flow nasal cannula (ie, oxygen delivered at ≤ 6 L/min) or blowby	Continue supportive care as per G1 and include IV fluid bolus and/or supplemental oxygen as needed Administer tocilizumab[42-44] 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours if no improvement in signs and symptoms of CRS; limit to a maximum of three doses in a 24-hour period, with a maximum of four doses total In patients with hypotension that persists after two fluid boluses and after one to two doses of tocilizumab, may consider dexamethasone 10 mg IV (or equivalent) every 12 hours for one to two doses and then reassess Manage per G3 if no improvement within 24 hours of starting tocilizumab
G3: Fever[a]: temperature ≥ 38°C not attributable to any other cause *plus* Hypotension: requiring a vasopressor with or without vasopressin *And/or* Hypoxia: requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Continue supportive care as per G2 and include vasopressors as needed Admit patient to ICU If echocardiogram was not already performed, obtain ECHO to assess cardiac function and conduct hemodynamic monitoring Tocilizumab as per G2 if maximum dose is not reached within 24-hour period plus dexamethasone 10 mg IV every 6 hours (or equivalent) and rapidly taper once symptoms improve If refractory, manage as per G4
G4: Fever[a]: temperature ≥ 38°C not attributable to any other cause *plus* Hypotension: requiring multiple vasopressors (excluding vasopressin) *And/or* Hypoxia: requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	Continue supportive care as per G3 plus mechanical ventilation as needed Administer tocilizumab as per G2 if maximum is not reached within 24-hour period Initiate high-dose methylprednisolone at a dose of 500 mg IV every 12 hours for 3 days, followed by 250 mg IV every 12 hours for 2 days, 125 mg IV every 12 hours for 2 days, and 60 mg IV every 12 hours until CRS improvement to G1 If not improving, consider methylprednisolone 1,000 mg IV 2 times a day or alternate therapy[a]
Additional considerations: Organ toxicities associated with CRS may be graded according to CTCAE v5.0, but they do not influence CRS grading CRS may be associated with cardiac, hepatic, and/or renal dysfunction Earlier steroid use appears to reduce the rate of CAR T-cell treatment-related CRS and neurologic events and is recommended for some products (axicabtagene ciloleucel or brexucabtagene autoleucel)[45-47] Strongly consider antifungal prophylaxis in patients receiving steroids for the treatment of CRS and/or ICANS	

ASCO = American Society of Clinical Oncology.
Santamasso BD, et al. *J Clin Oncol*. 2021;39(35):3978-3992.

As we progress, if you've given tocilizumab and you've given steroids, the DEX 10 mg IV, and the patient you feel is still having CRS symptoms, so someone with fever without localizing symptoms, or now is a little bit later in the ER and you swab them and all the viral cultures are negative. Maybe you sent a procalcitonin, and the procal is negative and you're not thinking that this is infection. The UA is negative, and the chest x-ray is negative, and the patient is developing gradual worsening of CRS, you can crank up the treatment. So in terms of steroids, you can go from Dex 10 IV q6 up to high dose solumedrol, a gram QD to BID up to every QD to BID up to 3 days. The next step would be the use of anakinra, the anti-IL1 monoclonal antibody, and if that doesn't work, remember the original lymphodepletion chemotherapy we gave for CAR T that kills T cells. You can give chemotherapy, drugs like cyclophosphamide to really shut down the T cells. At this point the patient is likely to be admitted and being mostly managed by the oncologist, but from an ER standpoint, tocilizumab, dexamethasone, and anakinra are tools that are well within your grasp to use.

ICANS Pathophysiology

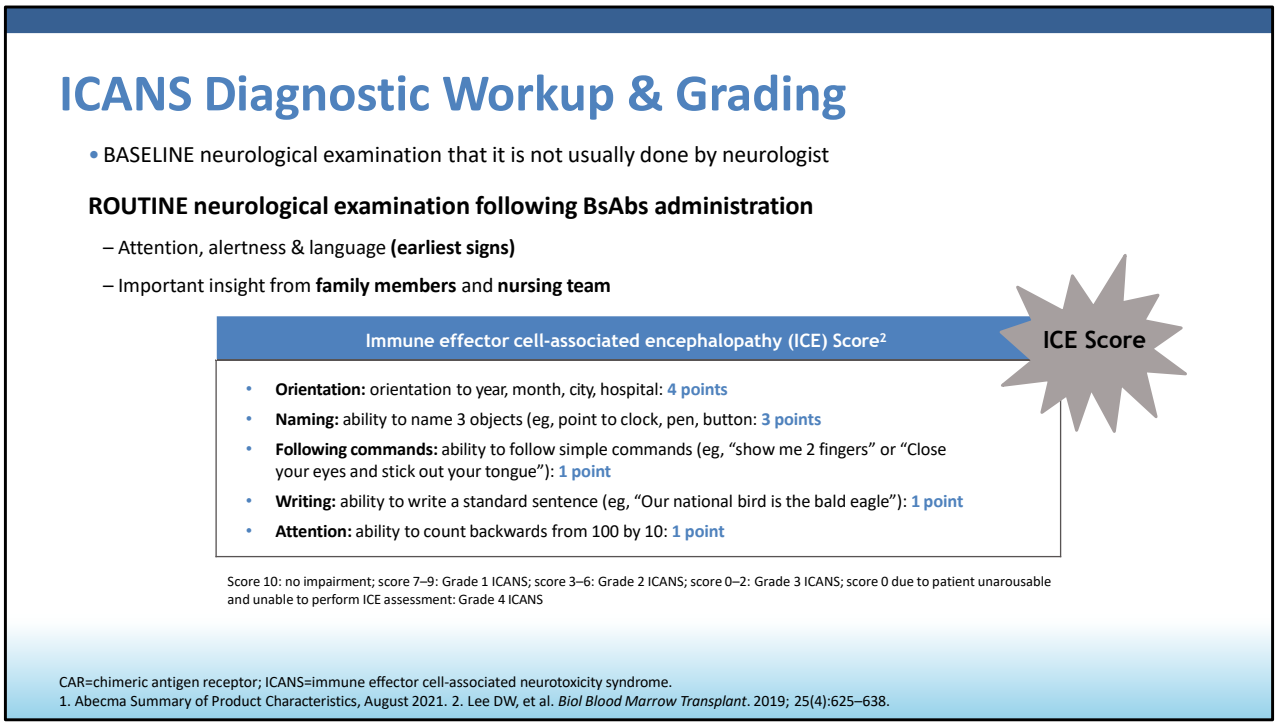


- CAR T-cells have the ability of penetrating into the CNS, crossing the blood-brain barrier
- BsAbs-related ICANS is mediated by the cytokynes released by T- lymphocytes, and the T-lymphocyte can potentially penetrate
- This can be related with the fact that after BsAb the incidence and severity are lower

Systemic inflammation and high levels of circulating cytokines → **ENDOTHELIAL CELL ACTIVATION and BLOOD-BRAIN BARRIER DISRUPTION** → **INFLAMMATORY CASCADE WITHIN THE CNS** → cortical and subcortical dysfunction +/- cerebral edema

CNS = central nervous system; ICANS = immune effector cell-associated neurotoxicity syndrome.
Morris EC, et al. *Nat Rev Immunol*. 2022;22(2):85-96.

ICANS has a little bit of a different pathophysiology. And that's where those T cells that we activate cross through the blood brain barrier and are now causing alterations in sensorium, everything from a headache, to a little confusion, to seizure, to comatose.



Now the way we evaluate this is with what we call the ICE score. So when I am on call and the nurse calls me about the patient getting a T cell engager in the middle of the night, they'll read me off the vitals and they'll say the ICE is 10 out of 10.

The ICE scores are 10-point scoring system, including orientation, naming, following commands, writing, and attention. The most important one of all of these is writing. So when we have patients in the hospital receiving T cell redirection therapy, we have them write a sentence every single day while they're in the hospital because one of the earliest signs of the development of ICANS is micrographia and dysgraphia. If you have a patient in the ER and they're a little bit off, have them write a sentence out and evaluate it, if it's really horrible, or really small, this may be indicative of ICANS.

ICANS Diagnostic Workup & Grading

ICE score | Level of consciousness | Seizures | Motor findings | Intracranial pressure

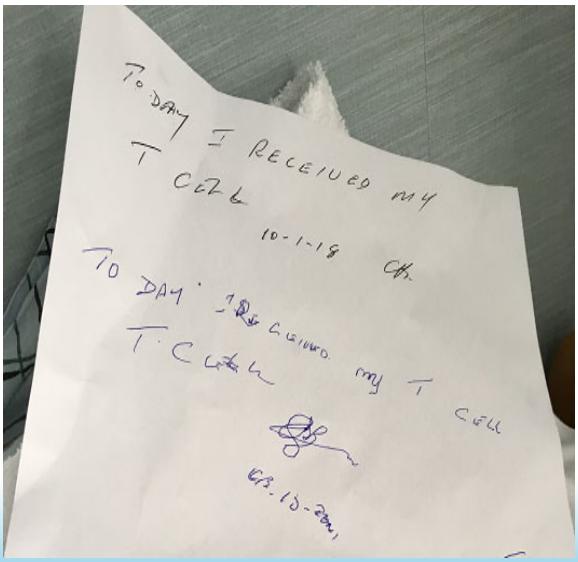
ASTCT ICANS Consensus Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7–9	3–6	0–2	0 (patient is unarousable and unable to perform ICE)
Depressed level consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure			Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis is or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
† Depressed level of consciousness should be attributable to no other cause (e.g, no sedating medication).
‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.
ASTCT; American Society for Transplantation and Cellular Therapy; CTCAE, Common Terminology Criteria for Adverse Events; EEG, electroencephalogram; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; ICP, intracranial pressure.
Lee DW, et al. *Biol Blood Marrow Transplant.* 2019; 25(4):625–638.

Now we have a grading system as well, and it really follows the ICE score. Again as you get progressive, this is something where you really want to start considering having the ICU involved. It's always a difficult call in the ER when someone hits the floor, you know, this patient is a little bit confused, a little bit somnolent. I think for some disorders you send them to a Gen Med floor, but if you have someone who has grade 2 or even grade 3 ICANS, this is someone who's going to need a higher level of monitoring.

Daily Sentence Is Key to Early Neurotoxicity Detection!!



So just to give you an example. This is a patient of ours that developed neurotox and on the first day they'll write 'Today I received my T cells." Looks great, and the second day it's starting to look like my handwriting, and today I can't read that at all. As this patient was writing this, they started to have more and more confusion, and ultimately developed full on neurotoxicity.

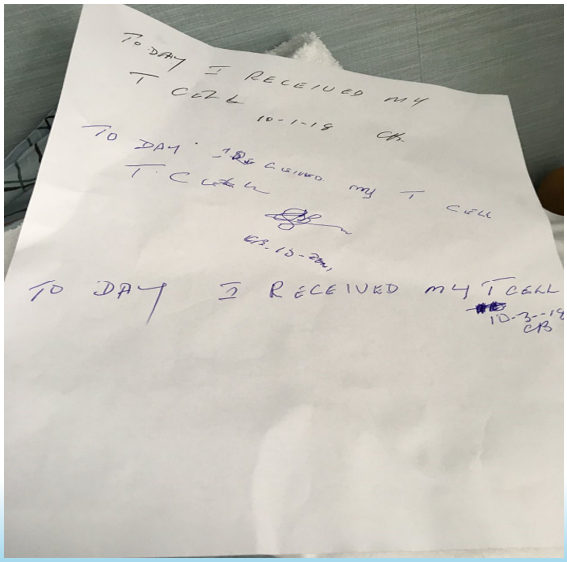
NCCN Guidelines: CAR T-Cell-Related Neurotoxicity Treatment

Treatment by Grade	No Concurrent CRS[x]	Additional Therapy if Concurrent CRS
Grade 1[v]	• Supportive care	Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose)[aa, †]
Grade 2	• Supportive care • 1 dose of dexamethasone 10 mg IV and reassess. Can repeat every 6–12 hours, if no improvement.	Anti-IL-6 therapy as per Grade 1[aa] Consider transferring patient to ICU if neurotoxicity associated with grade ≥2 CRS
Grade 3[w]	• ICU care is recommended • Dexamethasone 10 mg IV every 6 hours or methylprednisolone, 1 mg/kg IV every 12 hours[k,y] • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity.	Anti-IL-6 therapy as per Grade 1[aa]
Grade 4[w]	• ICU care, consider mechanical ventilation for airway protection. • High-dose corticosteroids[k,z] • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.	Anti-IL-6 therapy as per Grade 1[aa]

Thompson JA, et al. *J Natl Compr Canc Netw*. 2022;20(4):387-405.

Now, here's where the question of are they having CRS with the ICANS, or ICANS alone has a big impact. So it turns out that if you're having CRS and ICANS oftentimes, the first approach is going to be to either give dexamethasone or tocilizumab. However, if you are not having CRS when you have ICANS, there's no role for tocilizumab because Toci does not cross the blood brain barrier as dexamethasone does, and as anakinra does. In general, if you have either CRS with ICANS that's recalcitrant to Toci, or ICANS with no CRS, usually the first approach is to give dexamethasone. So 10 milligrams IV x 1 up to every 6 hours. And again, this is where someone who was brought in by a family member, they were told that they had a CAR T or a bispecific antibody a few weeks ago and reported some headache and they are now more somnolent, has a lowered ICE score, or a lower Glasgow Coma Index, something of that nature. Here the progression is the same approach, where you start slowly escalating from dexamethasone, considering high dose solumedrol or anakinra. Again one of the things you want to consider here is neuroimaging, and the patient with really depressed ICE scores, you may want to consider anti-epileptic drugs such as keppra, because these patients can seize and you may want to get neuro and/or ICU involved.

Normalization of the Handwriting



This patient received anakinra and dexamethasone and you can see their handwriting returned to normal.

ASCO Guidelines: Hemophagocytic Lymphohistiocytosis

Workup or evaluation[55]:
- CBC with differential and coagulation studies (PT, aPTT, fibrinogen, and D-dimer)
- Liver function tests (ALT, AST, GGT, total bilirubin, albumin, and lactate dehydrogenase)
- Serum triglycerides (fasting) and serum ferritin
- Soluble IL-2 receptor alpha (sCD25 or sIL-2R) and/or CXCL9
- The following testing should be performed in all patients, on the basis of the signs and symptoms of specific organ involvement and/or the degree of suspicion for the presence of HLH[55]:
  - Cultures of blood, bone marrow, urine, and CSF, and viral titers and quantitative PCR testing for EBV, CMV, adenovirus, and other suspected viruses. Follow levels of any identified virus during treatment with the appropriate antiviral therapy
  - Bone marrow aspirate and biopsy
  - Electrocardiograph, chest radiography, and echocardiogram
  - Lumbar puncture with CSF analysis
  - Brain MRI scan, with and without contrast. Imaging of the CNS may show parameningeal infiltrations, subdural effusions, necrosis, and other abnormalities

Grading	Management[14,56,57]
All grades	Offer supportive care Use corticosteroids if the patient is deteriorating or unstable Although data are insufficient to recommend a transfusion threshold, replacement of fibrinogen should be considered in patients with a fibrinogen level below 150 mg/dL Manage G ≥ 3 organ toxicity with IL-6 antagonist plus corticosteroids If insufficient response after 48 hours, consider adding anakinra[11,58,59] Etoposide could be considered in severe, refractory cases, although there is a lack of data in this setting and concern for effect on lymphocytes.[16,60] Intrathecal cytarabine, with or without hydrocortisone, may also be considered for patients with HLH-associated neurotoxicity

Santamasso BD, et al. *J Clin Oncol*. 2021;39(35):3978-3992.

One of the other things we started to see a recrudescence of, is something called hemophagocytic lymphohistiocytosis. I know it's a mouthful, we colloquially refer to this as HLH. This is literally where the immune system gets so activated that the macrophages start gobbling up and eating the other cells within the bone marrow. Although this is classically described as being a secondary manifestation of diseases like lymphomas and leukemias, we now recognize that the chemokine and cytokine activation of T cell activation in bispecific antibodies and CAR Ts can lead to macrophage activation, and ultimately macrophage activation leads to HLH.

These are patients that come in with sky high LFTs, ferritin that can often be greater than 10,000, pancytopenia; these are odd presentations, but early diagnosis is key. If someone is not feeling well after a CAR T or bispecific, couple weeks later they come in with a brand new pancytopenia and AST and ALT are in the several hundreds, ferritin is in the thousands, or tens of thousands, you have to be concerned about HLH. This is where we start in mostly with high dose dexamethasone and anakinra. If these patients don't respond to high dose dexamethasone and anakinra, we start considering classical chemotherapeutic agents like etoposide.

Conclusions

- The landscape of myeloma treatment has and is evolving rapidly
- The current standard of care includes T-cell redirection therapies such as bispecific antibodies and CAR-T
- Along with ongoing improvement in response rates comes new toxicity profiles
- Steroids can often provide acute clinical benefit in many settings of presumed immune-related toxicities
- Ongoing collaboration needed between Hem/Onc and ED

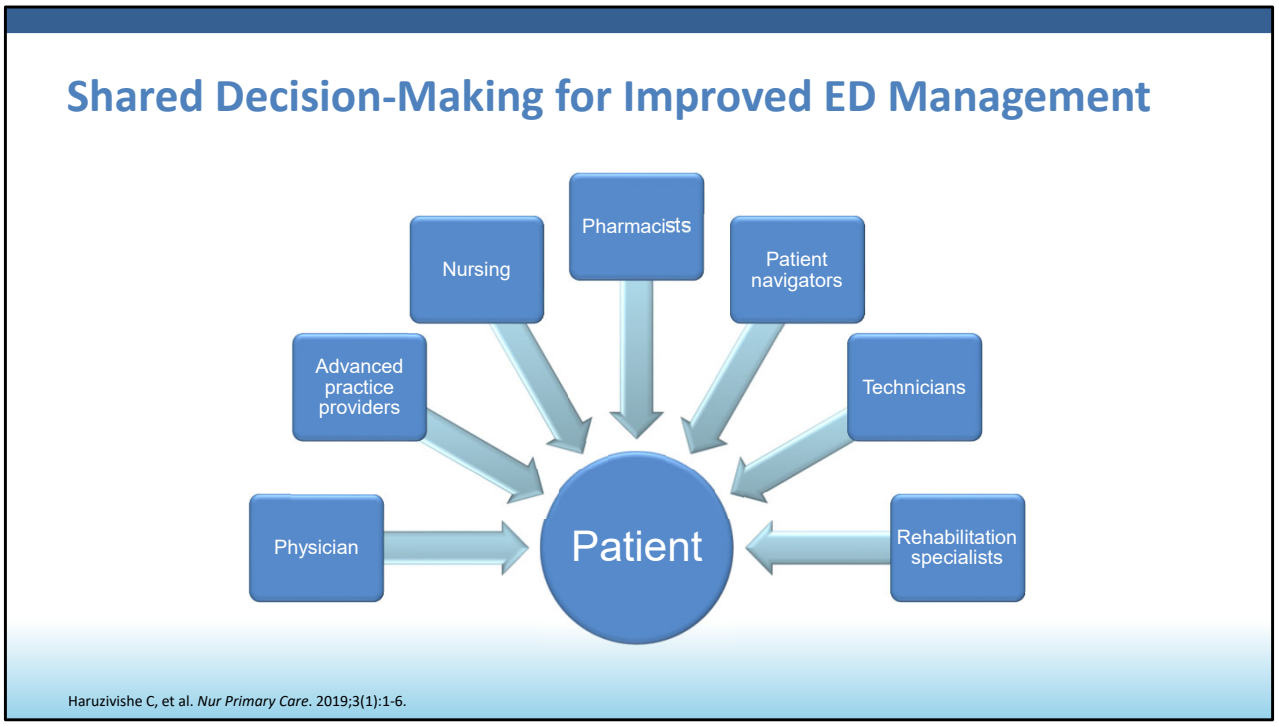
So ultimately, the landscape of myeloma has evolved. We've really come from, in my mind, the 3 great epochs of myeloma therapy. We started off in the 60s and 70s giving classical chemotherapy drugs, like alkylators and anthracyclines where response rates were quite poor, tolerability was horrible. And then at the turn of the millennium, we really started using what we call the novel therapies, the immunomodulatory drugs, the derivatives of thalidomide, the proteasome inhibitors and the monoclonal antibodies. But over the last few years we've moved on to the third great epoch of T-cell redirection with bispecific and CAR-Ts. Now, these are wonderful therapies, but at the time that we're talking right now the majority of these are being given in academic centers and not all ERs are in academic centers, but that doesn't mean that every patient who gets it at my center lives down the block. We have patients that travel a distance to get this, may be at home and may call 911 and these patients may enter your ER even if your institution does not give these therapies. Now CAR-Ts are still going to remain in the academic centers for a long period of time, probably forever, whereas bispecifics are slowly increasing in utilization in the community. The fact that these therapies are becoming much more ubiquitous, much more heavily utilized in the community means you're going to have to start knowing what to do with these patients.

You know in our ER I see them use the term cancer fever, and cancer fever means you have a malignancy you come in with a fever and here at our institution we have vancopime. I don't know if you guys have vancopime. And for those of you who are not familiar with this this is the combination of vancomycin and cefepime.

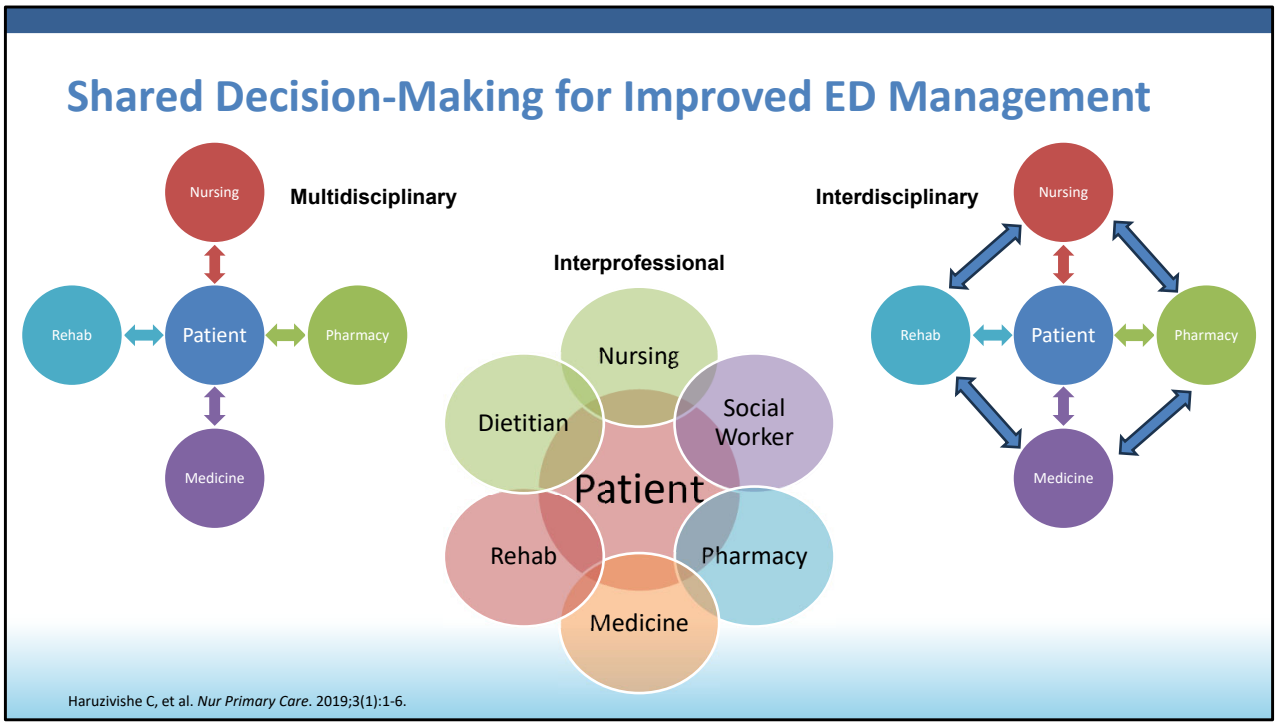
And it's very common that I come in when I'm on service in the morning and the residents present the case. Ah, Mrs. Jones came in last night. She had some fever, they drew cultures. They did scans and x-rays and urine, and she's on vancomycin and cefepime. And where that is pretty good for many of our patients, if that patient is having CRS or ICANS, they could be dead by the morning or severely impaired. So what do you do when these patients hit the ER? I think that as much information as you can gather about what therapy they're on and specifically asked if they're getting one of these new immune therapies. They may have a card, they may have a loved one with them. This is where I think early collaboration with the HEM/ONC doctor is very important. I like sleep as much as the next person, you don't have to wake me at 3 o'clock in the morning when my patient on therapy had a slip and fall and has a fractured ankle, but if there's a question, I would rather get that call at 3:00 am to help guide therapy.

In general, ICANS is going to be less common in the ER, but CRS is going to be more common. I think when in doubt this is where you know, I always joke that the dermatologist has two pockets, one pocket has a steroid cream, one has the antifungal cream; when they don't know they give both. I think the same could be true here. We do the same on the inpatient side. Someone has a fever within an hour of the drug, that's CRS. Months later, it's infection. But oftentimes we get patient a week or 2 in, can't tell, we draw a cultures. We give 10 of DEX. We give broad spectrum antibiotics and then we undergo an evaluation including things like procalcitonin and directed evaluation like chest x-ray and urine. The next morning the procal was 3 and the UA is positive. Yep. You don't have to give more steroids, that's infection. The next day the patient is improving not back to baseline, but the procal is normal and the cultures are all negative, that may have just been CRS.

A Multidisciplinary Team Approach to Care



The multidisciplinary team is the way to go here, and it's really important to involve everyone in this. Ongoing collaborations with not just the HEM/ONC docs, but the APNs, the RNs, pharmacists are critical, especially when giving multiple, very expensive and complex drugs. Patient navigators, technicians, and unfortunately rehab specialists, for patients that need it.



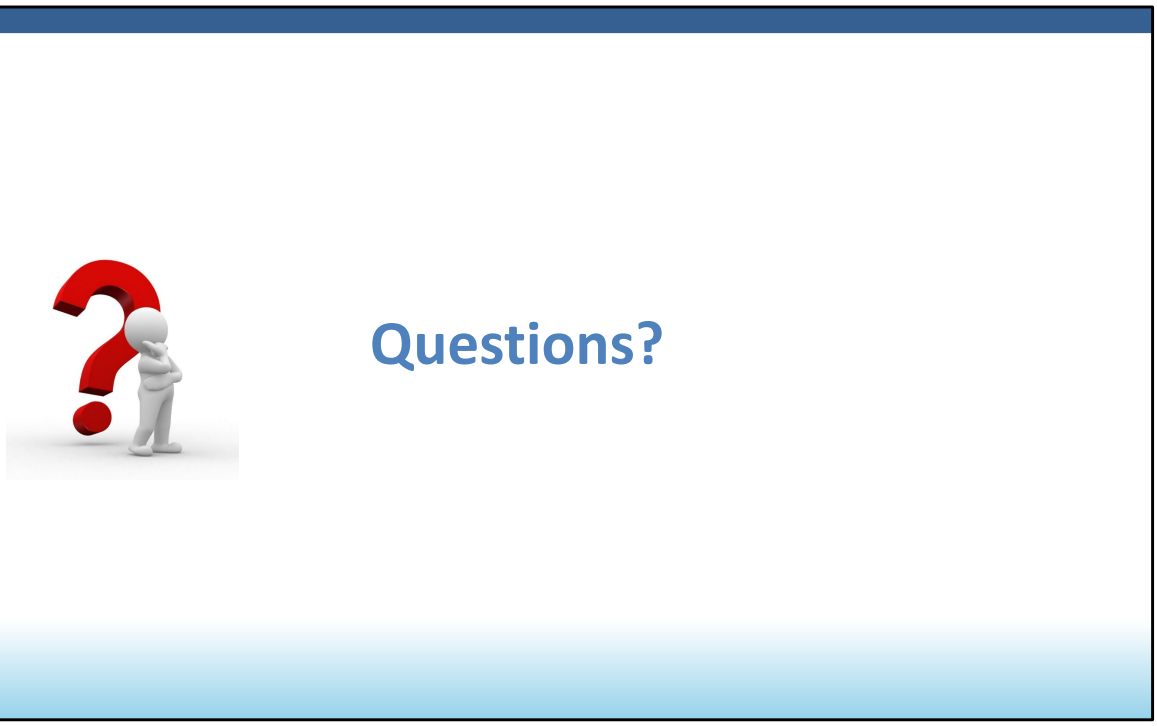
Ultimately having the patient centered and the focus in the middle, but including also people like dieticians because patients with the GPRC5D drugs may come in with weight loss. Having nutritional support may be absolutely critical for these patients.

ED Management Summary

- High clinical index of suspicion
- Calling consultants early
- Transferring to higher level of care early
- Ordering labs/images to help colleagues on admission

So I think the issue is having an index of suspicion, you know, someone comes in and they have right now these are mostly in the hematologic malignancies like leukemia, lymphoma, and myeloma, they haven't been really utilized much in solid tumors, but they are coming too. Someone comes in with a blood cancer, ask or inquire, or see if the EMR has any information about what drug they're on if that drug ends in a mab, ask and see if we can get more information because most of these are some type of antibody drugs that end in mab and a lot of them will have brand new side effects that we haven't seen in a generation gone by.

Calling consultants early and this is multifaceted. This is taking someone who's more somnolent and not just say I give them some fluid and observe them. You may need neurology for assessment of need for anti-epileptic therapy. We may need early ICU monitoring and I know in most institutions the board to be above for ICU admission is pressure support, or ventilatory support. Oftentimes these patients can become quite ill quite fast, and we have agreements with our ICU that anyone with advancing ICANS, even if they're not on pressors or ventilatory support can go to the ICU for more aggressive monitoring. Calling the HEM/ONC doctor who may be treating the patient earlier on to get an assessment of what is more likely in the scenario– overwhelming infection, CRS, ICANS. Could it be all 3? We've had patients with all 3 that need therapy for all 3. Ongoing labs and imaging to help narrow down “is this fever and tachycardia, sepsis, or is it CRS, or can we not tell at the current moment?”



And with that I will thank you everyone very kindly for listening and take any questions, concerns, complaints, or comments.

Moderator: Thank you so much Dr. Richter.

At this time, we are happy to take any questions that you may have.

Hi. I was just wondering what is the difference between the ICE score and the CARTOX?

So the CARTOX is really a general assessment for I believe CARTOX is more infection. That's evaluating the risk of infection with a CAR T, and that's kind of predictive values of what may happen during the CAR T. The ICE score is really when you think they're having ICANS itself. So someone who's already received the CAR T or maybe having a headache or confusion. That's where we really use the ICE score.

Moderator: And another question coming up.

Hi, are there any negative implications for giving antibiotics to these patients who are having cytokine release?

That's a really phenomenal question and the answer is no, and I think that's really our approach is that and both sides of the equation. So there's no harm in giving them antibiotics. Obviously without the general risk of antibiotics with allergic reactions, or rashes, or infection, or resistance, but there's no harm in shooting first and askig questions later for both antibiotics and steroids. I think for a while there were two reasons we worried about steroids in these patients. One, we're worried if they have overwhelming infection, will we further harm their immune system by giving steroids, and the answer is no you're not. The other is that we used to be very scared about giving steroids, especially to CAR T patients because steroids kill T cells and the worry was always “Oh my God, if you have a CAR T that cost a half a million dollars to manufacture, and it's this person's only hope at fighting their cancer and you give steroids, you could kill the CAR T.” It turns out that with 10 DEX, you're not going to kill the CAR T. And for bispecific antibodies, if for some reason you did harm the T cells, which you are not going to, you can get another dose in a few weeks. So, no issues giving either which is why I think in a realm where most ERs are not going to have easy access to tocilizumab, giving steroids and antibiotics is a great first approach for patients where you can't figure it out.

Moderator: With that I would like to thank you Dr. Richter for your time, your teaching, and expertise this evening.

