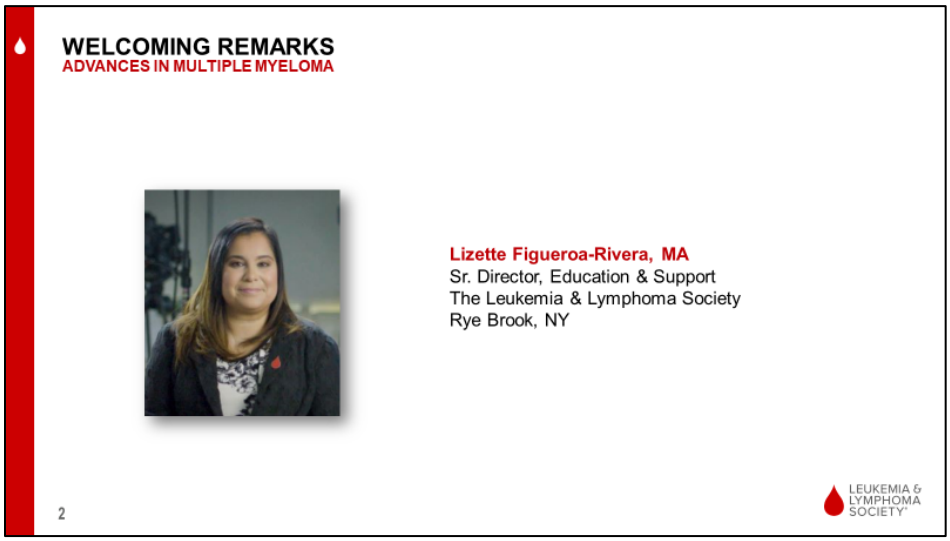
WELCOME AND INTRODUCTION

Lizette Figueroa-Rivera, MA

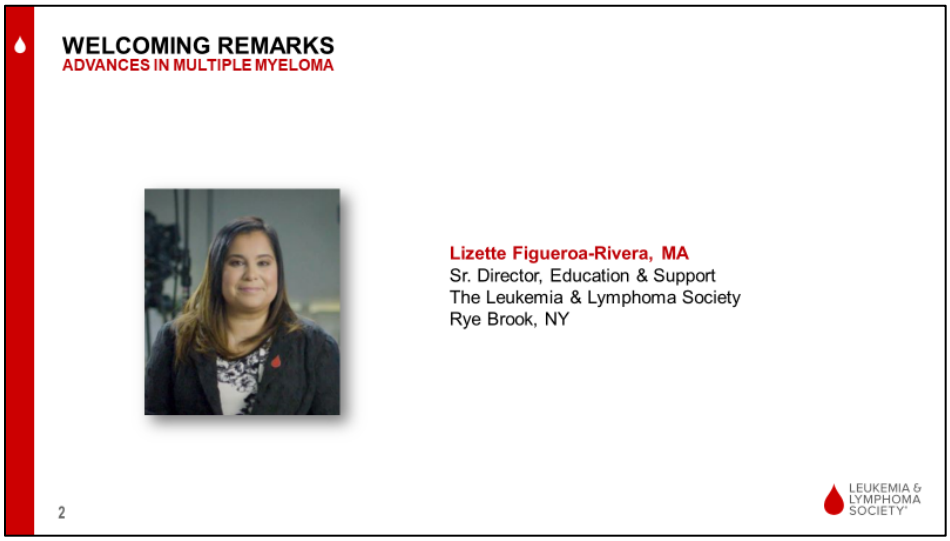
Thank you, and hello everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you.



Special thanks to Dr. Angela Dispenzieri for volunteering her time and expertise with us today. Dr. Warsame had an emergency and is not able to present today. So, thank you, Dr. Dispenzieri for being able to present this program for us today.

We have over 2,500 people participating in today's program from across the United States, as well as other countries, including Antigua and Barbuda, Canada, Colombia, Iraq, Mexico, Singapore, and the Vatican City.

We would like to acknowledge and thank Bristol Myers Squibb, Genentech & Biogen, GlaxoSmithKline, Legend Biotech & Janssen Oncology, and Oncopeptides for support of today's program. Following the presentation, we'll take questions from the audience.



We are also taping and transcribing this program for future posting on our website.

The Leukemia & Lymphoma Society, LLS, is a champion for myeloma patients, caregivers, survivors, and families. Together with our volunteers, patients, researchers, healthcare professionals, and supporters, we are determined to change the future of myeloma treatment and care.
Our vision centers on driving new breakthroughs and cures, helping all myeloma patients access the care they need to survive and thrive and addressing healthcare disparities that disproportionately impacts underserved populations.

Quoting our President and CEO, Dr. Louis DeGennaro, "Great progress has been made in multiple myeloma research. LLS continues to support research efforts that will help us better understand

multiple myeloma resulting in better and more effective treatments."

And as this program demonstrates, we are the leading source of free cancer information, education, and support, and we touch patients in their communities through our regional offices. LLS also acts as the voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them navigate their cancer.

In honor of March being Myeloma Awareness Month, you may want to become active in LLS's advocacy efforts to ensure that myeloma patients get the access to quality, affordable, and coordinated care by visiting www.LLS.org/Advocacy or text LLSACTION to 69866.

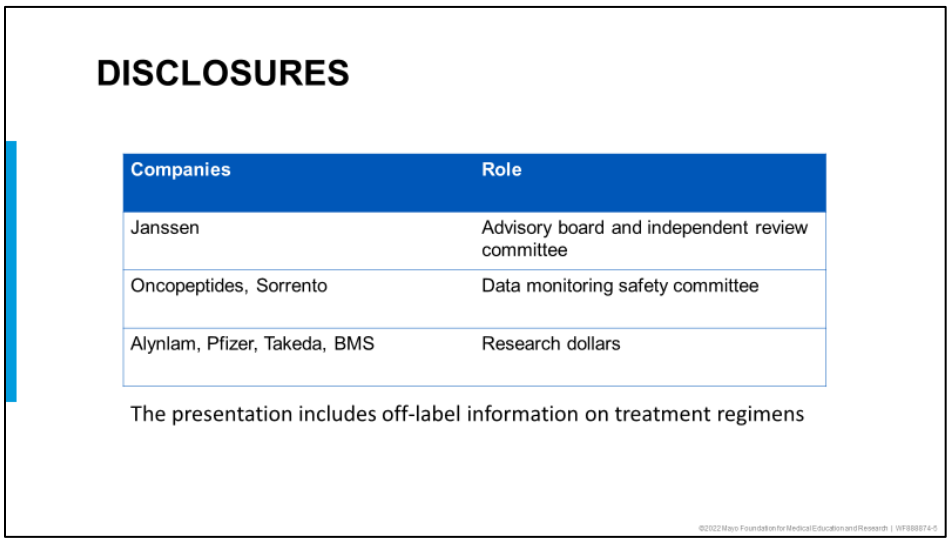
PRESENTATION

Lizette Figueroa-Rivera, MA

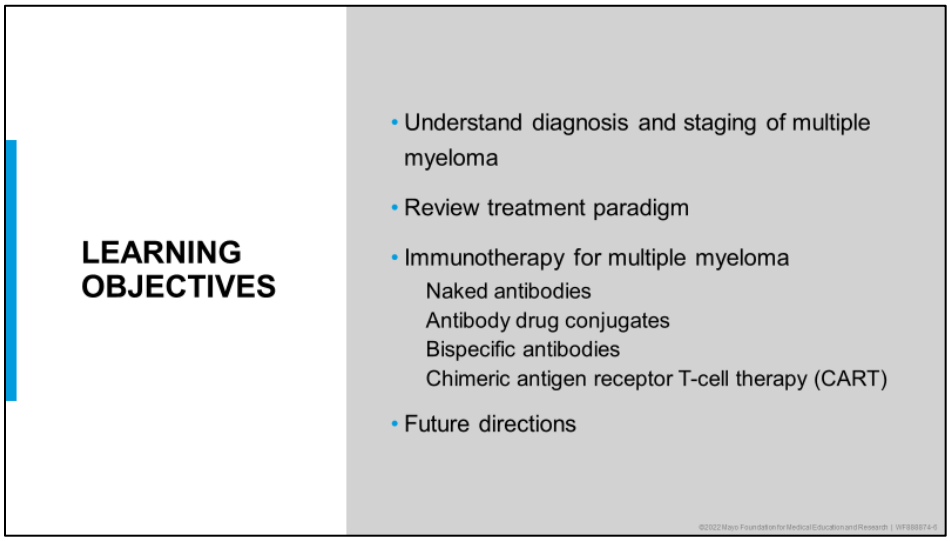
I am now pleased to introduce Dr. Angela Dispenzieri, the Serene M. and Frances C. Durling Professor of Medicine and of Laboratory Medicine, Research Chair, Division of Hematology at the Mayo Clinic in Rochester, Minnesota.

Dr. Dispenzieri, I'm now privileged to turn the program over to you.

Angela Dispenzieri, MD

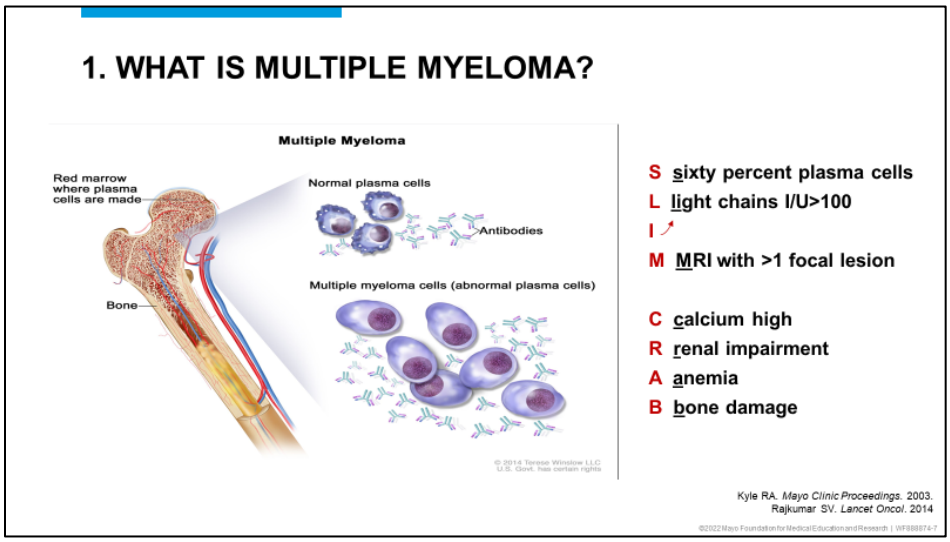


Well thank you so much. My disclosures are here but thank you to the organizers and thank you to LLS for all you do for our patients.



And so, yeah, I'm here instead of Dr. Warsame, so those of you who are expecting to see her, I'm sorry. You get me instead. But we have a good program today, and hopefully we can cover from the basics to some of the more exciting newer therapies.

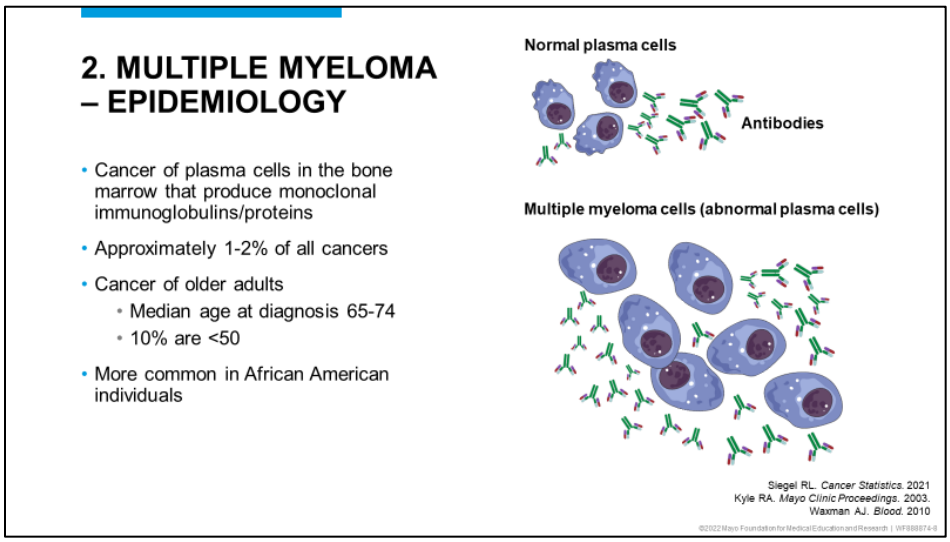
So, our goals today are really the diagnosis and staging of multiple myeloma, to talk about treatment paradigms, and most of our time will be focused on immunotherapy for multiple myeloma, which it's a whole slew of new drugs, some of which are FDA (U.S. Food and Drug Administration) approved, some of which will likely be FDA approved and available. And so, looking to a very bright future in this space.



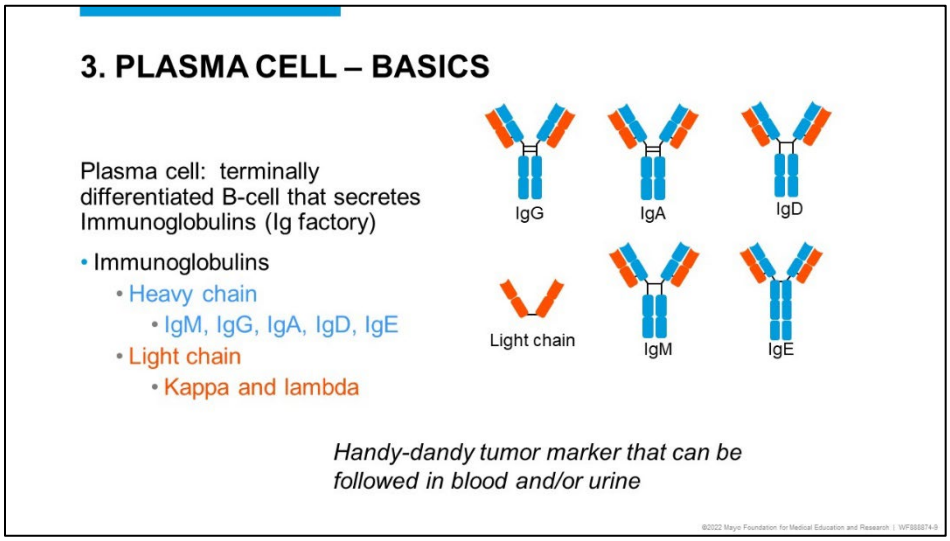
So, for some of you who are newer to the world of multiple myeloma, what is multiple myeloma? So, in the bone marrow, you can see there are a number of different kinds of cells. But the cells of interest to us in the world of myeloma are the plasma cells. And the normal function of plasma cells is to make antibodies to help us fight infection. When plasma cells go wrong and make too many of

themselves, instead of calling it plasma cell cancer, we call it multiple myeloma. And so, you can see those cells on this slide.

The definition of multiple myeloma, and if you look at the bottom right-hand corner, the old definition was CRAB, high calcium, renal impairment or kidney impairment, anemia, and bone damage. About seven or so years ago, eight years ago, that definition was broadened to also include in the definition of multiple myeloma, those patients who had at least 60% bone marrow plasma cells or the immunoglobulin free light chains of greater than 100, the magnetic resonance imaging (MRI) with more than one focal lesion. Because as you may or may not know, there's a precancerous state before multiple myeloma or two states. One is called monoclonal gammopathy of undetermined significance (MGUS), which the majority of people who have that do not go on to develop myeloma, but they have these same proteins circulating in their bloodstream; and then smoldering myeloma. So, these definitions help differentiate the precancerous kind of conditions from the kind of condition that we want to treat.



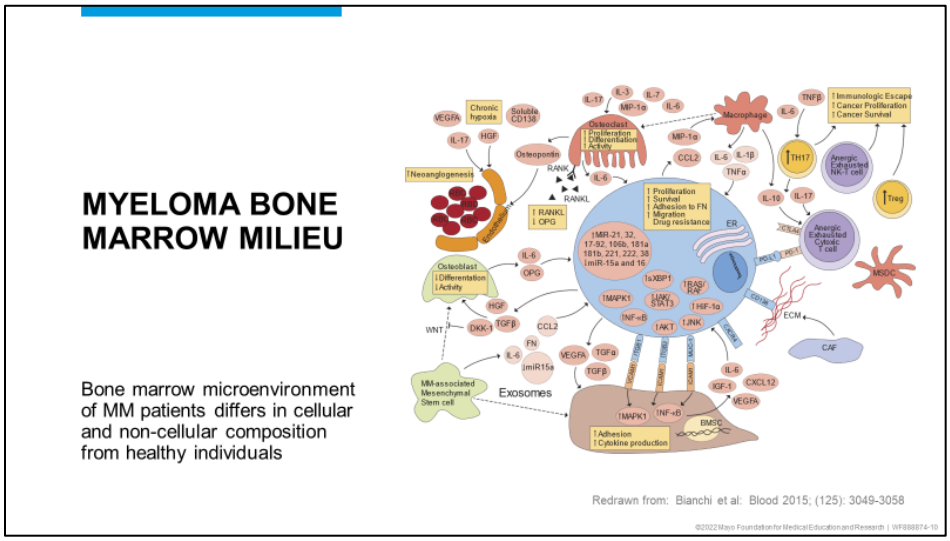
So, again, I've already said it's a cancer of plasma cells in the bone marrow. It's about 1 to 2% of all cancers, so not terribly common. It affects older adults most commonly, so the median age is really around 70. About 10%, however, are under the age of 50. And it is more common in African American individuals than Caucasian or Asian people.



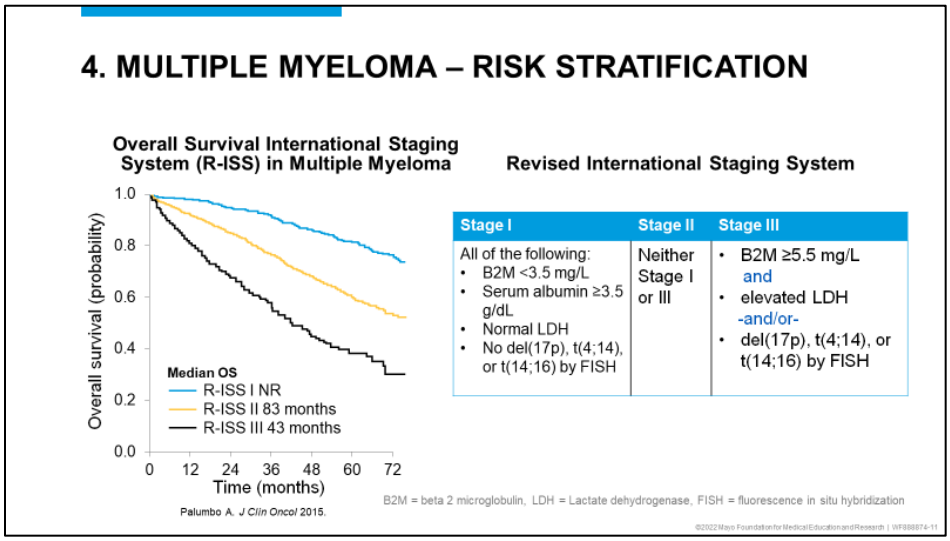
So, a little bit about the basics. So I told you that there are these plasma cells, a kind of cell that lives in the bone marrow; and they're kind of a B-cell, and their job is to make immunoglobulins or antibodies. And what you see to the right are cartoon representations of the different type of immunoglobulins that exist. And basically, an immunoglobulin has a heavy chain or two heavy chains, which are characterized in blue on this slide, and then two light chains, which are characterized in orange.

And the heavy are bigger, so they're heavier; and the light chains are smaller, and so they're light. But then we further separated, there are sort of two flavors of light chains. There's the kappa and the lambda, and each patient will have either a kappa or a lambda light chain, not typically both. And then the heavy chain, they get to select from the menu of these five. So, immunoglobulin G (IgG), IgA are the most common. IgG's most common, then IgA. IgD is only about 1%. And then some patients don't have heavy chain, so that's just light chain myeloma we call it. It's very rare to have an IgM heavy chain and even more rare to have an IgE. But these are the kinds of things that your doctor will talk to you about and say, the myeloma protein we're following is, for example, an IgA kappa.

And so, the handy thing about the fact that these plasma cells that live in the bone marrow, that they make these immunoglobulins, is that these proteins serve as tumor markers that can be followed in the blood and/or urine, so people don't have to have as many bone marrow biopsies. We can see how the disease is moving along, whether in a good direction, a bad direction, etc. Most often just with simple bloodwork.



Now myeloma-complicated disease-and, again, I'm not going to go through this in the middle, is the representation of a plasma cell and sort of different pathways that are activated. But the point of this slide is it's living in an environment in the bone marrow where there are a number of other types of cells that actually relate to the myeloma, sort of feeds off of, that contribute chemicals we call cytokines; and so, they're really complex interactions. And these different interactions offer opportunities for intervention. And as we talk about the immunotherapy, as we go down later towards the right upper portion of the slide, we have things called T cells; and those are things that we're going to be modifying to help treat multiple myeloma.



So, what about staging or risk stratification? So, up until, I don't know, ten years or so, we used just what was called the ISS, the International Staging System, which we looked at something called beta-2-microglobulin and also serum albumin, and that was a staging system that was used. And there was a I, II, III. But about ten years ago it became increasingly obvious that the chromosomes of the patients' myeloma cells were very important as well; and so, we wanted to feed that into our staging system for patients with multiple myeloma. And so now there's the Revised International Staging

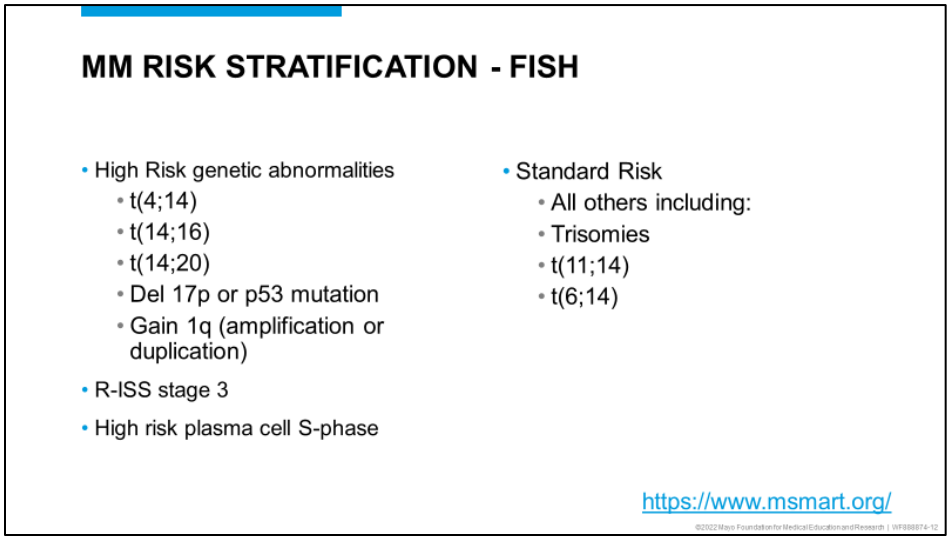
System (R-ISS). And the components there are the blood tests, beta-2-microglobulin, serum albumin. Also, LDH (lactate dehydrogenase), which is just an enzyme in the blood; but then these different genetic changes that are specific to the patients' myeloma cells.

And so, Stage I is having low values of the beta-2-microglobulin, higher levels of the serum albumin, and a normal LDH and the absence of these cytogenetic findings or genetic findings. In contrast, Stage III is represented by a very high beta-2-microglobulin, and either an elevated LDH and/or one of these chromosomal abnormalities. And then Stage II is it doesn't satisfy either of the others.

And the purpose for these staging systems, again, when somebody's diagnosed with multiple myeloma, we don't have tea leaves. We cannot see the future for one patient, but these systems actually work pretty well for groups of patients. So, I always tell my patients I can't tell you what your destiny is going to be. If I had 100 people and if they had numbers like you, I'd do pretty well to guess what the average outcome for that group, how they would behave, but I can't tell for the one individual.

And so, when we do the staging system, then we get a better sense as we talk from doctor to doctor and trial to trial to know how well therapies work. And it just gives us just an overall sense of how patients' disease is going to behave. And so, what's shown here, and again these are old data by now, but you can see here that the blue line is the Stage I patients, the black line, or the Stage III patients, and the yellow is the Stage II. But there is a difference. The higher up that this curve is up on the right, the better the overall survival. So clearly the patients with the Stage I disease do better than those with the Stage III disease.

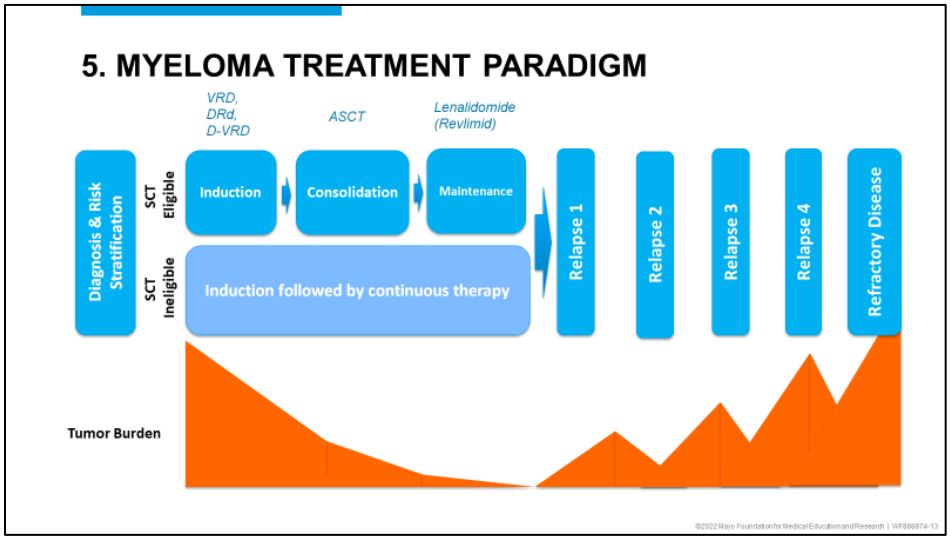
But there are definitely patients at this Stage I who do less well than patients with Stage III and vice versa. So it just goes to show how much we need to learn, and so it's helpful. But as a patient, I wouldn't focus on it too much. But it's nice to know what the doctors are talking about.



And so, the risk stratification in terms of just looking at the chromosomal kinds of things and things that are really specific to those myeloma cells themselves, we talked about what are called these translocations. So, t(4;14), t(14;16), t(14;20), deletion 17p, or p53 mutation. And also, now it's

recognized that gain and especially amplification of chromosome 1 or chromosome 1q also puts a patient at slightly higher risk. And then here, obviously, the R-ISS includes these cytogenetics; so, it's kind of repetitive on some level.

And then if a physician orders the right test and they look at the proliferation rate or the S-phase of the myeloma cells, that's also important. And then standard risk or really there can be some genetic changes; but trisomies and these other translocations don't put patients in this sort of higher risk category.

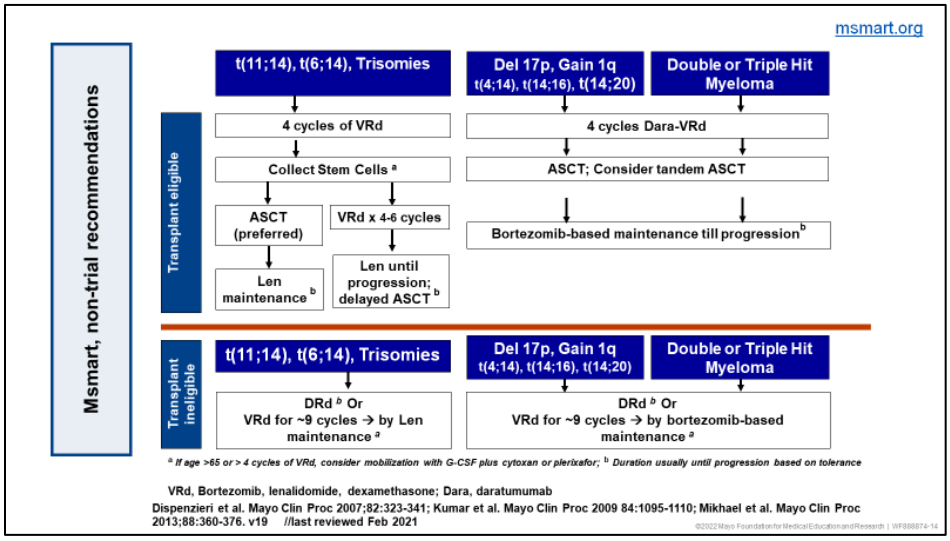


And so, from the bird's-eye view or the thousand-foot view, how do we approach treating multiple myeloma? So first, we want to make a diagnosis as you can see all the way on the left. And then in our minds, we typically break it into whether we think that the patient is eligible for stem cell transplant, or other people call it bone marrow transplant, or if they're ineligible. And, in general, we consider the ineligible patients are people that are in their mid-to-late 70s or people who have a lot of other illnesses or comorbidities. We don't consider that as an option.

But if you look at the upper piece here, if they're stem cell transplant-eligible, we break it down into induction, which is usually around four months of a particular kind of chemotherapy. The transplant itself is a consolidation strategy, so it's just more chemotherapy and then a maintenance approach. For those that are not eligible, it's typically induction followed by continuous therapy, which is kind of a maintenance strategy. And in the orange, you can see here tumor burden, right? When a patient is first diagnosed, they have lots of myeloma. But as the therapy goes, we reduce the amount of myeloma in the patient and hopefully make it almost disappear; and someday, hopefully, we'll make it disappear for everybody forever. But we're not quite there yet.

And so here I have showing, some of the induction strategies for those patients doing transplant. A real favorite for patients who are not undergoing transplant is daratumumab, (Darzalex®) lenalidomide (Revlimid®)-dex (dexamethasone/Decadron®). But here's transplant. And then the most standard maintenance is lenalidomide.

But once this has all happened, unfortunately, patients can relapse. And so, you see in orange the disease burden is going up, and so what do we do? We treat. And again, for some period of time, the patient will remain in remission. And if they relapse again, we treat again. And again, hopefully, we don't ever get to this place where it's refractory (when a disease does not respond to treatment) and nothing's working for us. But unfortunately, that can occur. And that's why research is so important so that we find more and more solutions. We have patients that are on their tenth line of therapy because they go through one thing and another, and hopefully there's always another therapy. Or better yet, we'll get it right the first time; and we'll be curing our patients.

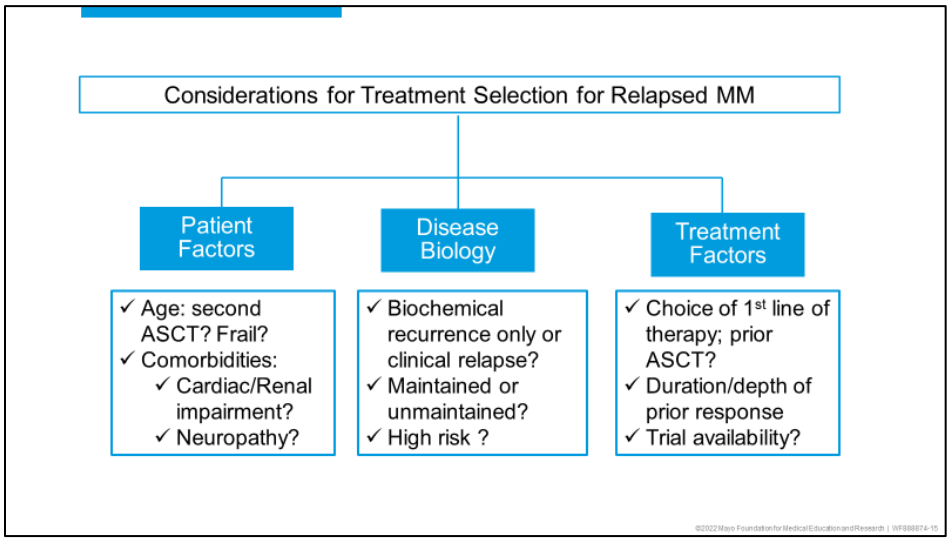


And so, this is just a very complicated slide. Above the line is patients who are transplant patients. Below the line are patients who are not. We tend to break it a little bit by the cytogenetic risk in terms of which regimens. We post online at mSMART.org what our current thinking is. I tell my patients I have good news and bad news about therapy for multiple myeloma. The good news is we have lots and lots of options. The bad news is we have lots and lots of options. And the reason it's good news is because the more treatments we have, we have Plan A, Plan B, Plan C, etc. to treat the myeloma. The bad news is that you're going to hear different opinions because there's so many new options, and we haven't followed patients ten years with a particular strategy. So, we can't tell you if Plan A is necessarily better than Plan B sometimes, and that ambiguity can cause stress for patients. But I think it's still overall really good news, and we just have to live with that ambiguity.

And so again, we tend to start with VRd or bortezomib-lenalidomide-dex (dexamethasone) or (by trade name) Velcade®-Revlimid®-dex, do stem cell collection. We tend to go down the transplant lane and then go to lenalidomide maintenance. But again, you could argue because the data are such that not everybody, even if you are transplant-eligible, has to have a transplant. And you could continue with some of the same therapy and then go to maintenance and then salvage with transplant.

So, the thing that we feel very strongly about is that if you are somebody who's transplant-eligible, even if we opt not to do transplant early on, to collect those seed cells and have them in the freezer available so that you have that strategy available to you. For patients who have the higher risk cytogenetics, then in those instances we tend to really lean more heavily on the transplant. Sometimes you can consider doing back-to-back stem cell transplants, so transplants separated by a

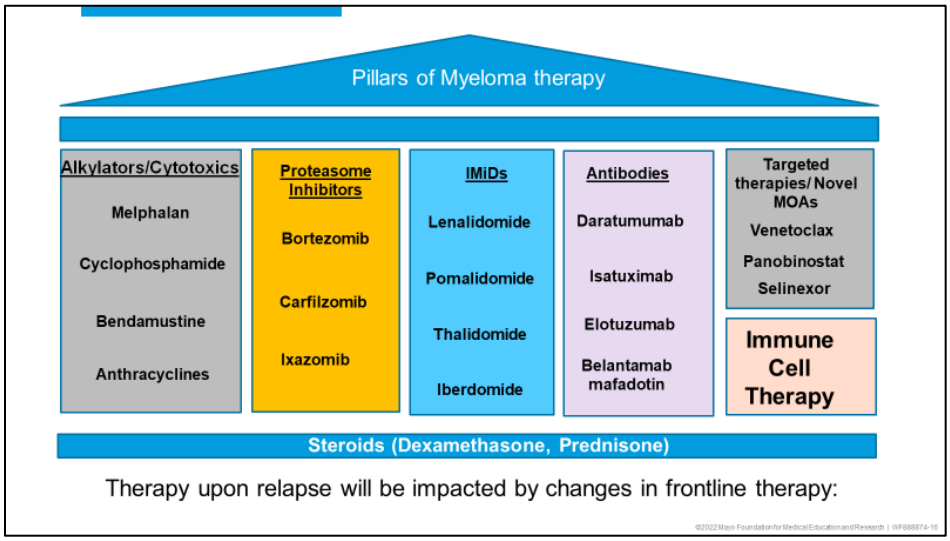
couple of months. And then we will typically use Revlimid (lenalidomide) and bortezomib as part of a maintenance strategy.
And then for the transplant-ineligible patients, we tend to go with DRd (daratumumab-lenalidomide-dex). One could use isatuximab (Sarclisa®)or daratumumab Rd. One could use another CD38 (cluster of differentiation 38) antibody like isatuximab-Revlimid-dex. And even VRd, though the Velcade (bortezomib) can be harder in older patients sometimes. And so, there's a lot of different ways of going about it.



So, when the patient relapses, then how do we decide? And a lot goes into that decision because there are patient factors. Is the patient frail? Do they have a lot of other medical problems? Just because the person has multiple myeloma, it doesn't mean that they can't pull the short straw for having coronary artery disease or other types of problems. So all these play a role in our choices. Whether they have neuropathy, either related to prior treatment or just they have a neuropathy for another reason.

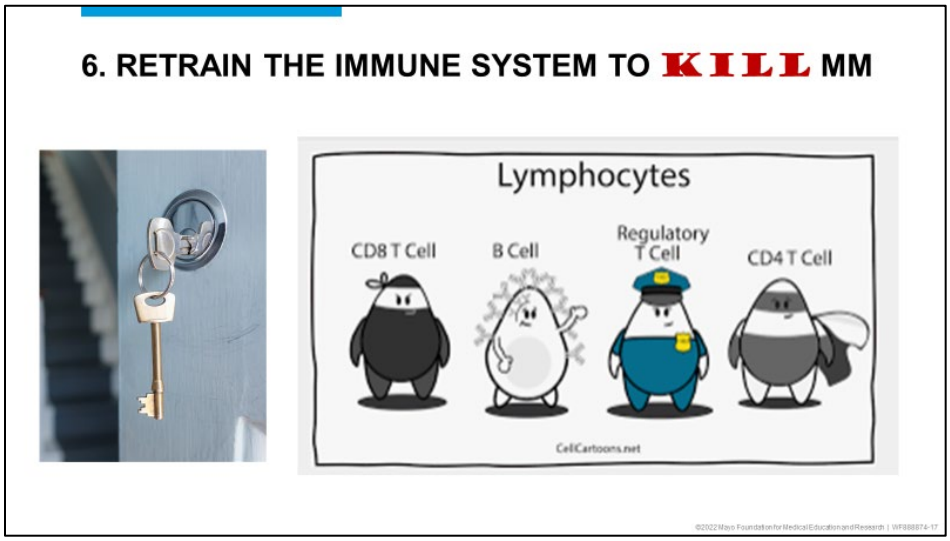
We think about how fast is the patient relapsing? Are they relapsing on maintain therapy? Unmaintained therapy? Did they have high-risk features at the beginning, or do they have high-risk features now? And then we also think about what have they had previously? And that will color what choices we make.

And of course, we really like to do clinical trials because, again, there are all types of trials. There are phase III trials which are comparing known really good therapies; but we're not sure if treatment A is better than treatment B. And we want to be able to reduce that ambiguity for the next sort of generation of patients. So, we will sometimes do a trial with Dr. X's favorite versus Dr. Y's favorite and sort of then see, how did the side effects compare, how does the time to next therapy compare, how does the overall survival compare?

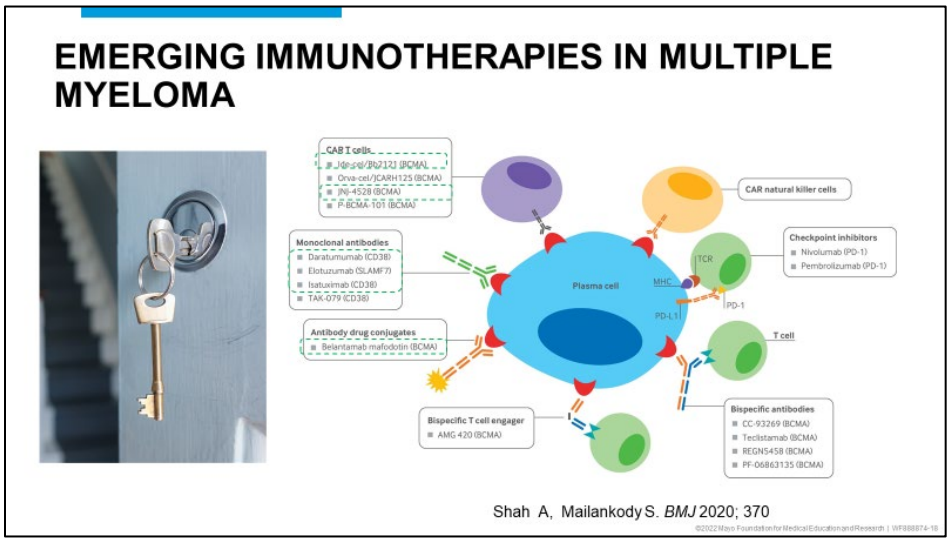


So, lots of different medicines here, and they have multiple names. Here we have the generics, so melphalan (Alkeran®), cyclophosphamide (Cytoxan®), bendamustine (Bendeka®), and then anthracyclines are some of the older fashioned medicines, but they still have a role. There are proteasome inhibitors, so bortezomib, also known as Velcade; carfilzomib, also known as Kyprolis®; ixazomib, known as Ninlaro®; lenalidomide, known as Revlimid; pomalidomide, known as Pomalyst®; thalidomide (Thalomid®); Iberdomide, which is not approved at this point; daratumumab or Darzalex®; isatuximab; elotuzumab (Empliciti®); and belantamab mafodotin which is Blenrep.

And then there's some other different targeted therapies, venetoclax (Venclexta®), which is not approved for multiple myeloma but works in a subset of patients. Selinexor (Xpovio®) is another kind of targeted therapy. We don't really use much panobinostat (Farydak®)anymore. But what's really very exciting is immune cell therapy, and so we're going to spend a fair amount of time talking about that kind of a strategy and also some different antibody therapies that are not necessarily approved at this point but have a lot of promise.



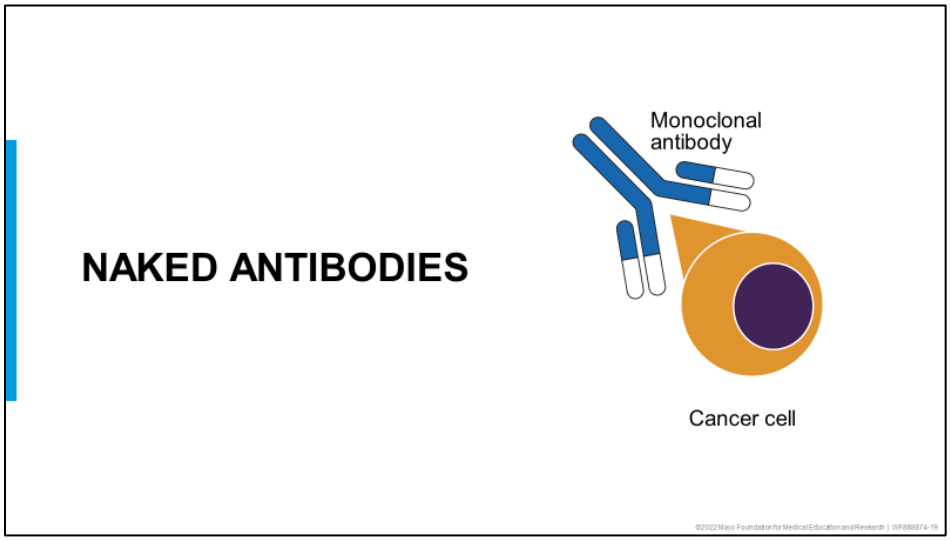
So, the idea here is to retrain the immune cell system to kill multiple myeloma; and there is, again, kind of a cute cartoon, but a number of different types of immune cells, B cells, T cells, and they have their own different roles. But the thing about using the immune system to kill myeloma, usually when we're using the immune system or at least the therapies in the myeloma space, they're very targeted. And it's sort of the ideas that the specific therapy or antibody or CAR T cell (chimeric antigen receptor T cell) or whatever, it's approaching the myeloma kind of the way a lock and a key fit together, that not just any key is going to fit in a given lock. And so, you're really trying to have it as a very precise type of therapy so that, hopefully, there's less collateral damage so to speak but also really just trying to hone in and kill myeloma cells.



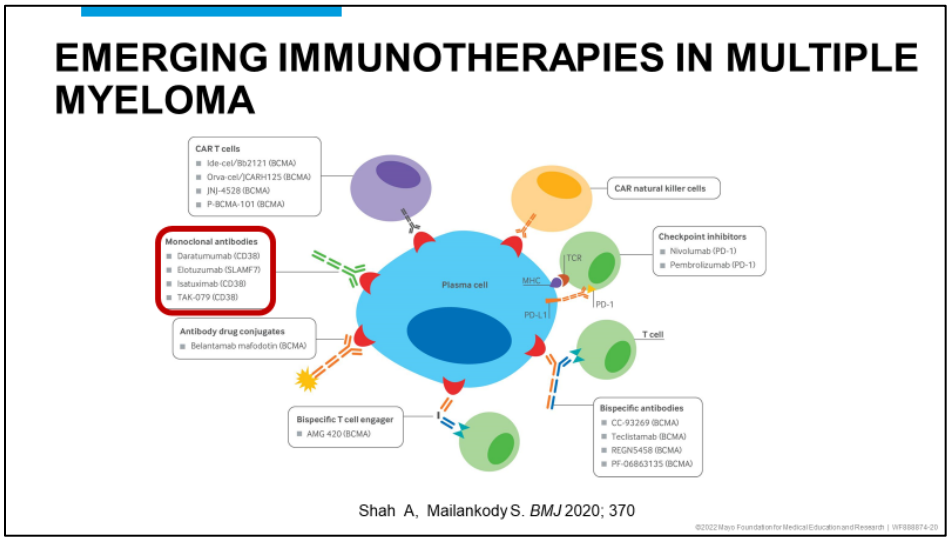
So, this is a busy slide that we're going to kind of go through piece by piece with the different strategies, but I think it's a nice representation. So here in the middle is a plasma cell, which is the myeloma cell, the cancer cell. And the myeloma cell has a coating, has a lot of different proteins and things on it; and here they're represented as these little red blobs which then are on the outside of the

cells so they could be recognized by these different immune types of targeting agents to identify myeloma cells.

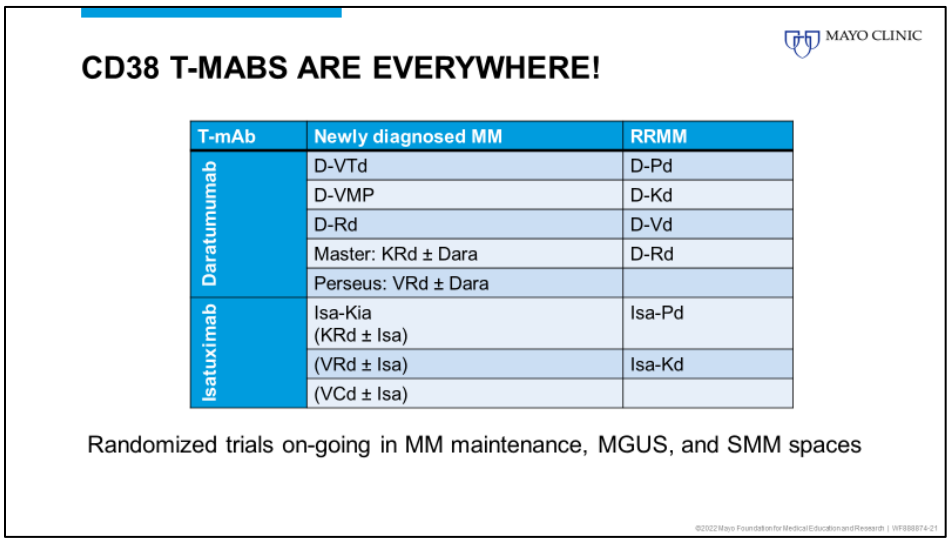
And the best targets are these little coatings, these little orange things that, hopefully, there's none of these orange things on other types of cells so we don't get what's called off-target toxicity, so to speak. And so, we have things like the monoclonal antibodies, which is kind of right here in the middle left. And those are the daratumumab, the elotuzumab, the isatuximab which are approved; and they can be given off the shelf. And they're recognizing different coatings on the cell, so daratumumab and isatuximab are both recognizing something called CD38. Elotuzumab recognizes something called SLAMF7 (signaling lymphocytic activation molecule). If you go under that in a counterclockwise fashion, there's Blenrep, which is an I suggest 'anti-BCMA (anti-B-cell maturation antigen), it targets BCMA. We have T-cell engagers, which is the next thing along the line and bispecific antibodies. We're going to skip past the checkpoint inhibitors and the natural killer cells because there's really not a lot there in the myeloma space. But then all the way at the top left, we have CAR T, and two of those are now FDA approved.



So, what are these things? So we'll start with the naked antibodies, and here we have the cancer cells. So, this orange thing is the myeloma cell, and then this sort of orange pointy thing is, basically, is part of the coating that the monoclonal antibody, so the therapeutic monoclonal antibody can recognize and help kill those cells.

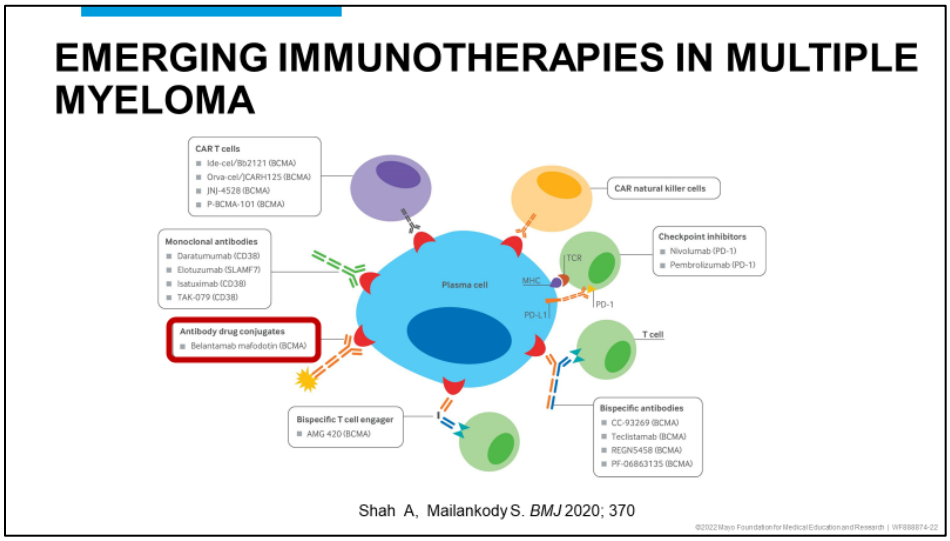


And so again, I already shared with you in red here, these are those therapies; and there's tons of daratumumab being used and tons of isatuximab being used at this point.

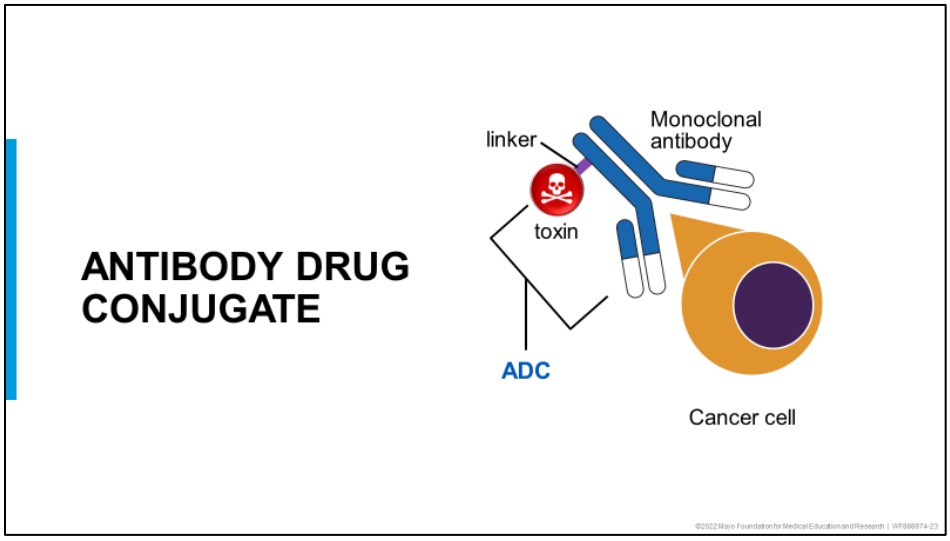


T-mAb	Newly diagnosed MM	RRMM
Daratumumab	D-VTd	D-Pd
	D-VMP	D-Kd
	D-Rd	D-Vd
	Master: KRd ± Dara	D-Rd
	Perseus: VRd ± Dara	
Isatuximab	Isa-Kia (KRd ± Isa)	Isa-Pd
	(VRd ± Isa)	Isa-Kd
	(VCd ± Isa)	

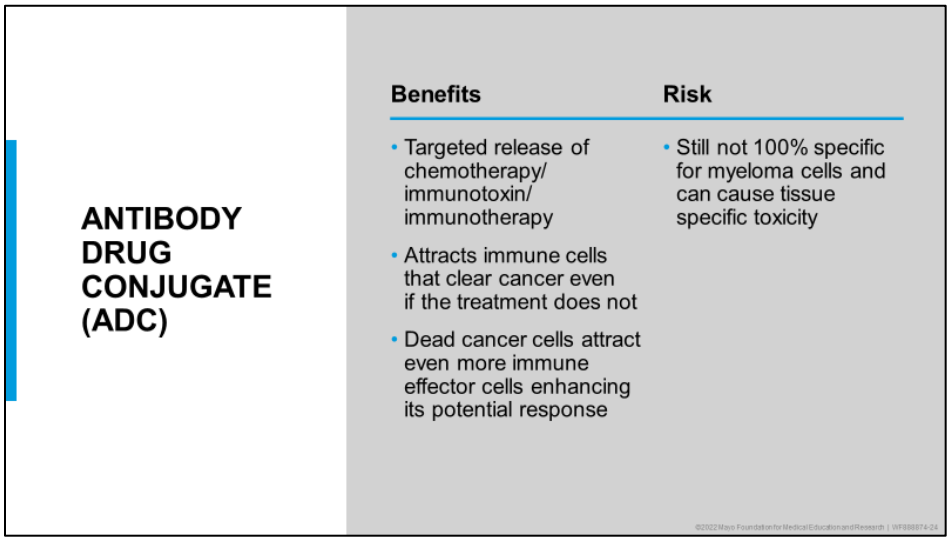
And so, these are CD38 therapeutic monoclonal antibodies, and there's a total alphabet soup in terms of combinations that these antibodies are being used with. So, in newly diagnosed multiple myeloma, it's being used with Velcade-thalidomide-dex, Velcade-melphalan-dex, Velcade-Revlimid-dex, etc., used with carfilzomib-Revlimid-dex. Daratumumab is added on with Velcade-Revlimid-dex. Isatuximab is being used with all of these other combinations, very similar to the above in the newly diagnosed setting; and also in the relapsed setting, you can see all these combinations that are in trials and various ones are FDA approved as well. So these are sort of almost old news at this point but wonderful drugs.



And so, I'm going to move now really into the more innovative, newer space. So, we have these, what we call antibody drug conjugates.

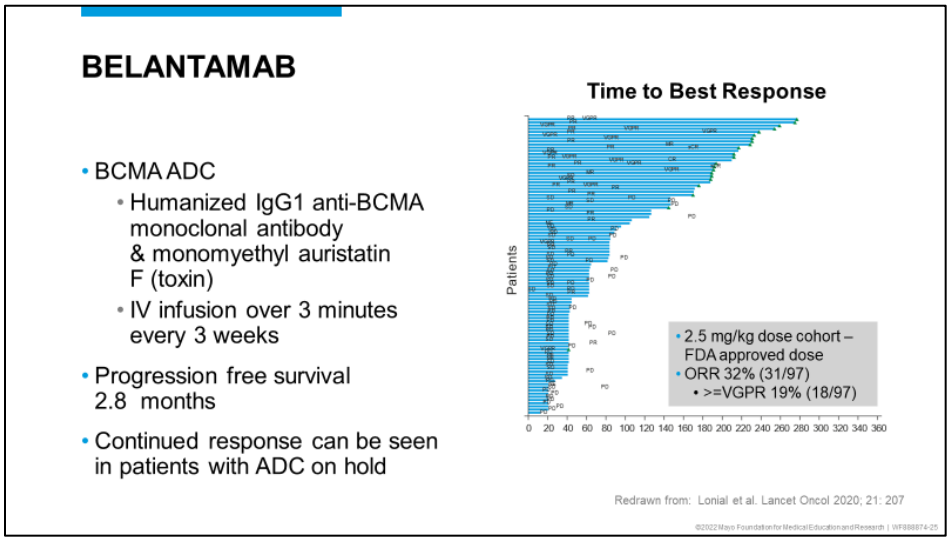


And so, what that is, very similar concept. You're recognizing something on the surface. In the case of Blenrep, this little triangular-shaped thing is going to be BCMA. And you have this similar antibody, but that antibody has attached to it a toxin. So, the idea is that you're bringing a toxin directly to the cancer cell, so not only are you going to kill it through just the antibody, the way antibodies kill cells, cancer cells and myeloma cells in this setting or even like they kill germs because, again, that was their normal function, but when we make them into drugs, we're trying to make them kill cancer cells. You're going to have that sort of immune-mediated means, but they're also adding a toxin, so you're like hand-delivering extra poison to kill that myeloma cell.



And so, the benefit of these antibody drug conjugates, or ADCs, is that you have this targeted release of either a chemotherapy or a toxin or some immunotherapy. Just like the other naked antibodies, you're attracting the immune cells that clear the cancer. And then also as you start killing cells, the myeloma cells, some of the debris actually attracts more of the immune cells to come and kill off what's going on there.

The risk with these antibody drug conjugates is that they're still not 100% specific for myeloma cells, and so they can cause specific toxicity.

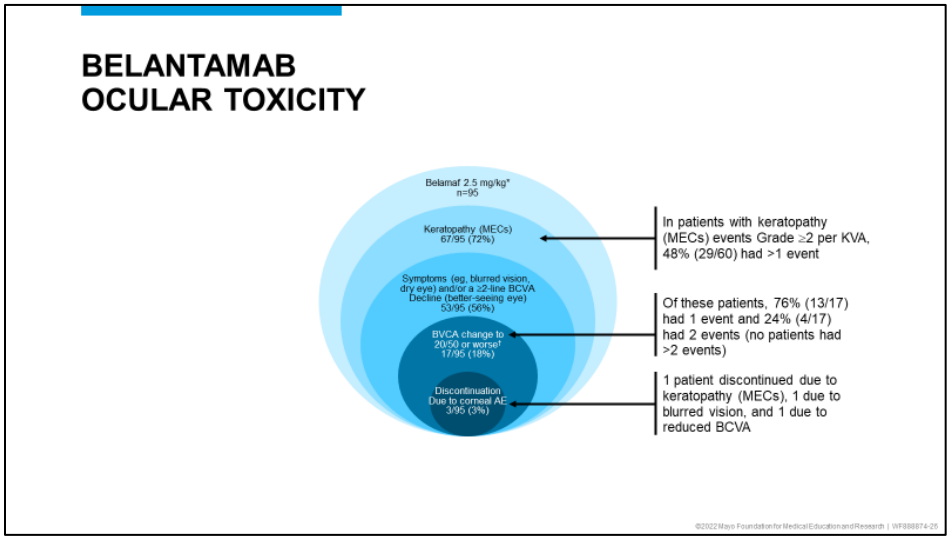


So what do I mean by that? So, we'll talk about belantamab (Blenrep), which is FDA approved. This is the targeted attacks is BCMA or B-cell maturation antigen; and the toxin attached to it is this monomethyl auristatin F (MMAF) toxin, and it's given IV.

In terms of the progression-free, so heavily pretreated patients, it's only a few months. And the thing is here though you can see this is what we call a swimmer's plot on the right-hand side, and time in

days is listed on the bottom. And each blue line is a patient, and so you'll see, here's a patient all the way at the top who's going on for about a year. And then if you look at the bottom, there are patients that really lasted, it helped only or it didn't help; and it lasted only for a month or something along those lines.

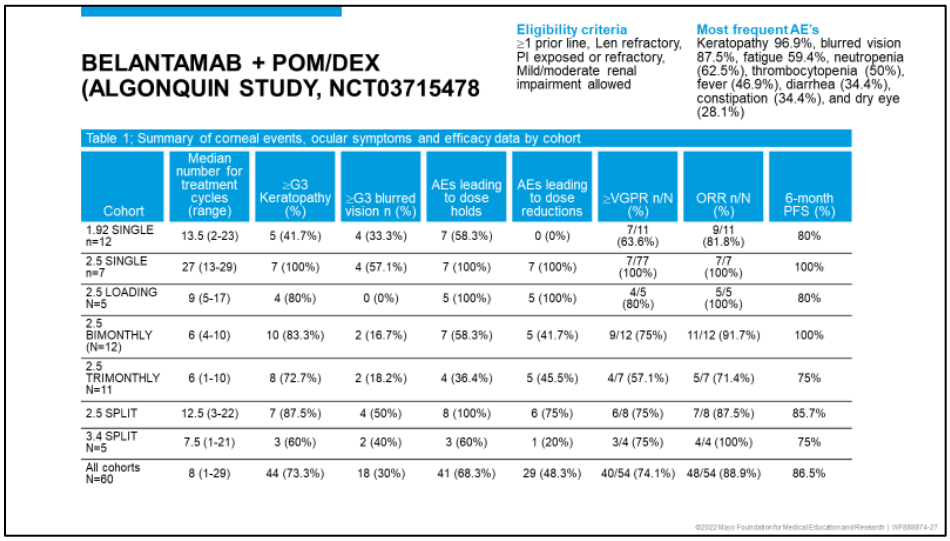
So again, responses in about a third of patients, the duration of response, at least in very heavily pretreated patients, is not as long as we would hope. But it is another treatment, and if you're one of the people at the top of this graph, that's really great.



The problem with this drug is that there is some off-target effect, and it's ocular or eye toxicity. And so, patients who are taking this drug need to have eye exams basically before every treatment, so kind of monthly eye exams, just to make sure that their corneas aren't being irritated.

And so, the majority of patients will have some amount of irritation to their eye. Of these, however, most are asymptomatic. It's more something the eye doctor sees than actually is causing symptoms. So, here they talk about 48% of patients in this cohort had at least one event of some kind of keratopathy (non-inflammatory disease of the cornea); and then of those, three-quarters had two events and so on. It's rare for patients to discontinue, so if you focus on the dark blue circle in the middle, one patient discontinued due to the keratopathy, one due to blurred vision, one due to reduced kind of vision issues.

So again, there's some room for improvement with this drug.



BELANTAMAB + POM/DEX (ALGONQUIN STUDY, NCT03715478

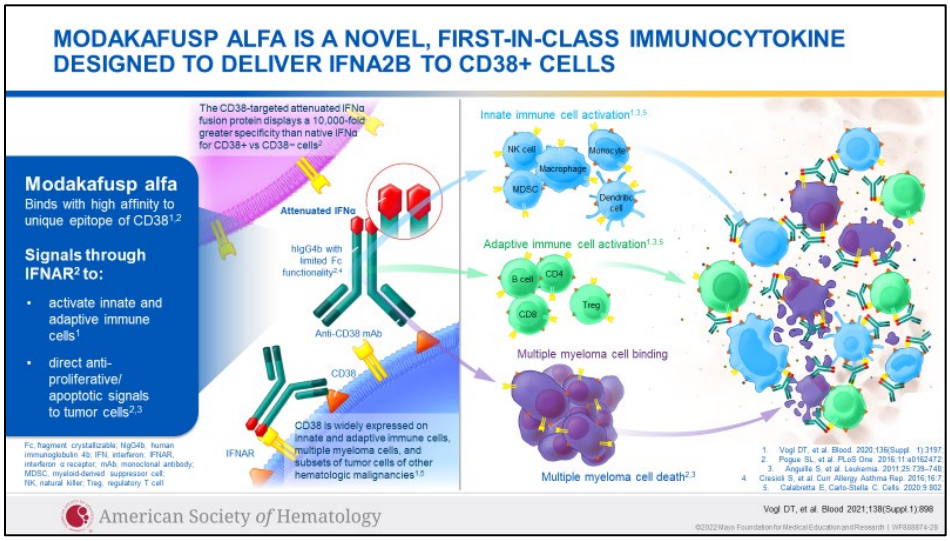
Eligibility criteria
≥1 prior line. Len refractory, PI exposed or refractory. Mild/moderate renal impairment allowed

Most frequent AE's
Keratopathy 96.9%, blurred vision 87.5%, fatigue 59.4%, neutropenia (62.5%), thrombocytopenia (50%), fever (46.9%), diarrhea (34.4%), constipation (34.4%), and dry eye (28.1%)

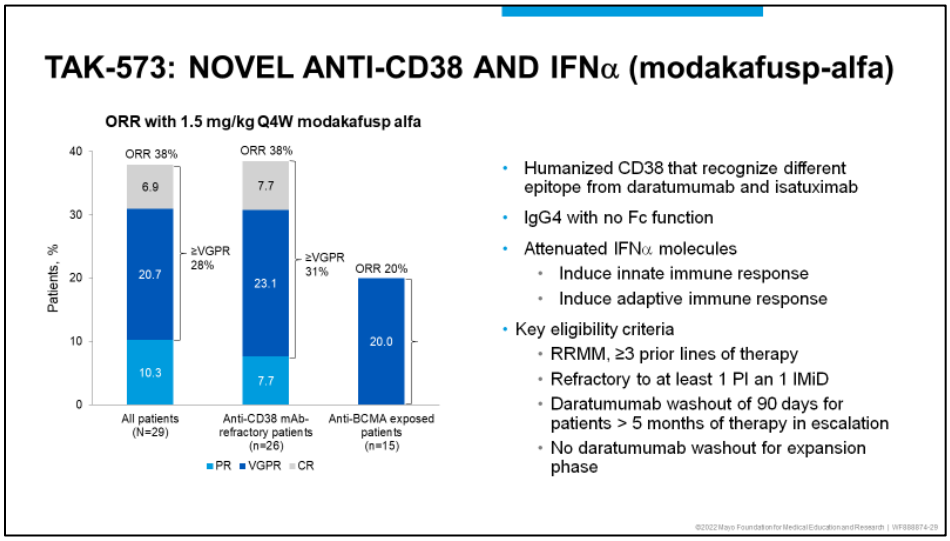
Table 1: Summary of corneal events, ocular symptoms and efficacy data by cohort

Cohort	Median number for treatment cycles (range)	≥G3 Keratopathy (%)	≥G3 blurred vision n (%)	AEs leading to dose holds	AEs leading to dose reductions	≥VGPR n/N (%)	ORR n/N (%)	6-month PFS (%)
1.92 SINGLE n=12	13.5 (2-23)	5 (41.7%)	4 (33.3%)	7 (58.3%)	0 (0%)	7/11 (63.6%)	9/11 (81.8%)	80%
2.5 SINGLE n=7	27 (13-29)	7 (100%)	4 (57.1%)	7 (100%)	7 (100%)	7/77 (100%)	7/7 (100%)	100%
2.5 LOADING N=5	9 (5-17)	4 (80%)	0 (0%)	5 (100%)	5 (100%)	4/5 (80%)	5/5 (100%)	80%
2.5 BIMONTHLY (N=12)	6 (4-10)	10 (83.3%)	2 (16.7%)	7 (58.3%)	5 (41.7%)	9/12 (75%)	11/12 (91.7%)	100%
2.5 TRIMONTHLY N=11	6 (1-10)	8 (72.7%)	2 (18.2%)	4 (36.4%)	5 (45.5%)	4/7 (57.1%)	5/7 (71.4%)	75%
2.5 SPLIT	12.5 (3-22)	7 (87.5%)	4 (50%)	8 (100%)	6 (75%)	6/8 (75%)	7/8 (87.5%)	85.7%
3.4 SPLIT N=5	7.5 (1-21)	3 (60%)	2 (40%)	3 (60%)	1 (20%)	3/4 (75%)	4/4 (100%)	75%
All cohorts N=60	8 (1-29)	44 (73.3%)	18 (30%)	41 (68.3%)	29 (48.3%)	40/54 (74.1%)	48/54 (88.9%)	86.5%

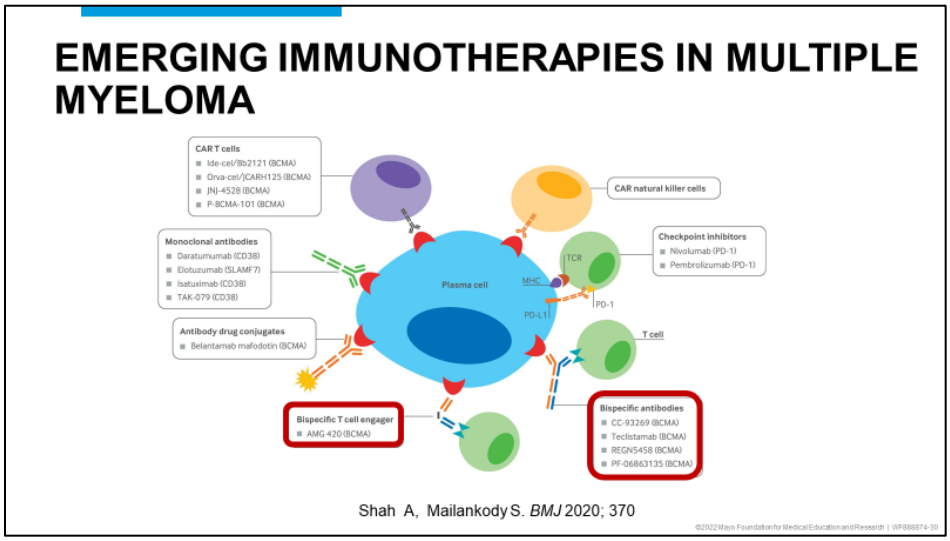
And the way that improvement is happening, very busy slide, but the idea here is to remind me of two things. Number one, it's being combined with other drugs, but also what they're doing, if you look at the left-hand column, is that we're looking at different schedules to see if we can have less eye issues and as much efficacy by using a reduced dose, by using it less frequently. And that looks promising, so more to follow in that space.



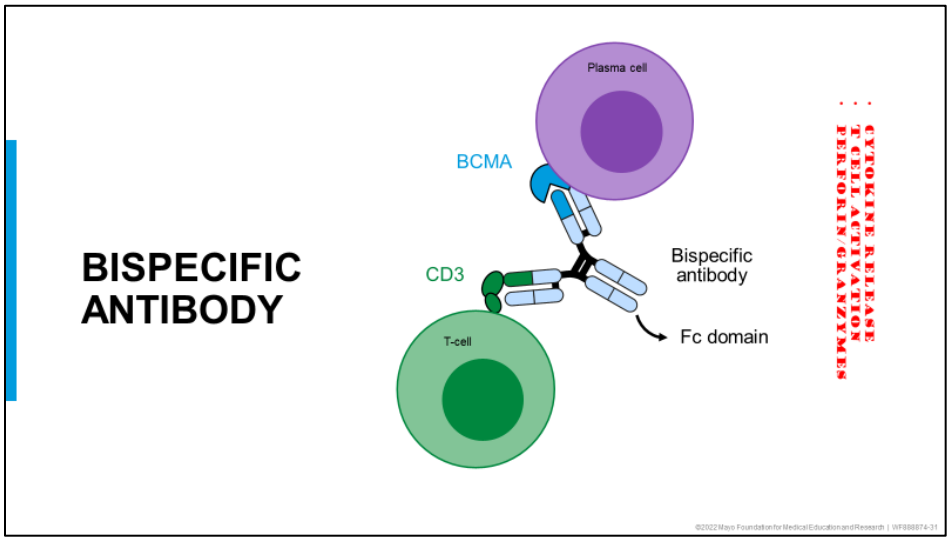
Here's another ADC, so this is an antibody drug conjugate. So, a drug called modakafusp alfa, but basically what it is, is its target is CD38, so it's not BCMA like Blenrep is. It's targeting the coating on the cells, CD38, like daratumumab does. But attached to this protein, if you look at sort of the bottom lower left, you see that there's something in red there. It says IFNAR (interferon-alpha receptor). It basically has sort of modified interferon at the edge of the tip of it, and it's delivering interferon, which stimulates the immune system further. So, you have the antibody recognizing the myeloma cell. But then there's the sort of stimulating agent there as opposed to a true toxin. And so, the thinking, if you look to the right of the cell, is that you end up with all these different types of immune reactions to hopefully kill more myeloma.



This is not FDA approved; it's in studies. But you can see in this bar chart to the left the name before that fancy name is TAK-573, which is actually easier to say. But for all patients, so the first bar you can see that the overall response rate is 38%. So more than a third of very heavily pretreated patients can respond and deep responses in more than 25% of patients. If you look at patients who had prior CD38 antibody therapy, so like daratumumab or isatuximab, you see that they actually had really good responses, even though they were refractory (not responding to treatment). And so that looks very promising.

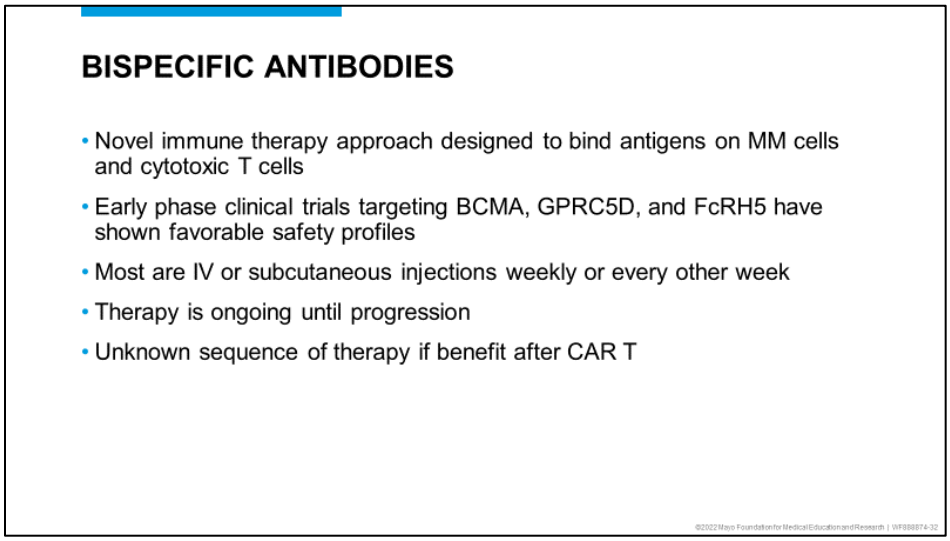


The next category that we're going to go to is really these bispecific antibodies.



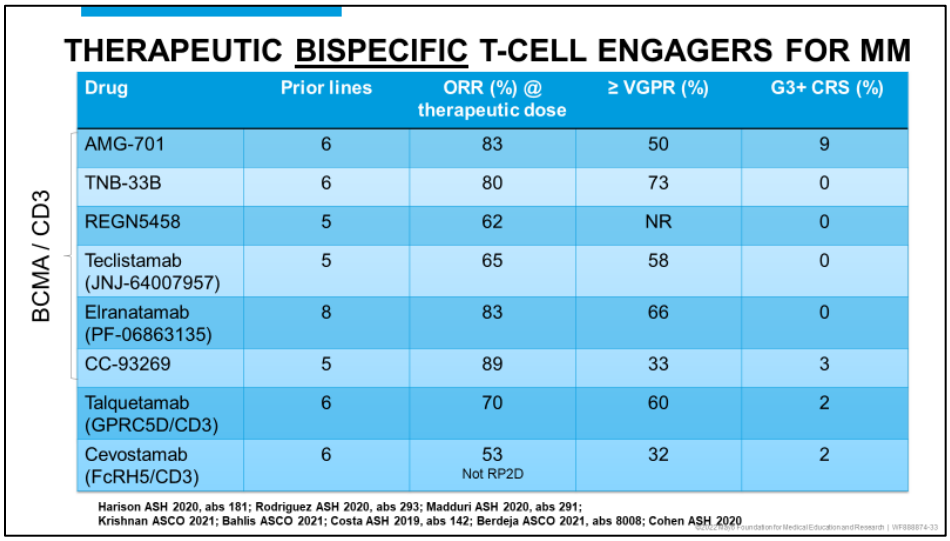
And so again here this is a cartoon. Here's the plasma cell or myeloma cell in purple up at the top. And the little blue thing is the BCMA. That's part of the myeloma cell. For example, BCMA, because a lot of the bispecifics are against BCMA, but it can be other things as we'll discuss. So, here's the, like one of the little coatings on the myeloma cell. You have this therapeutic antibody called a bispecific antibody; and what it does is if you imagine it's like kind of a person with two arms, one arm, it grabs onto the myeloma cell, and the other arm grabs onto the patient's own circulating T cells which are immune cells that should be killing myeloma. And it kind of says here, "Look, kill it." It's trying to stimulate the T cell and bring it in close proximity to the myeloma cell so that it can hopefully train the myeloma cells that are in the patient's body to kill myeloma.

And so, issues with this approach, you end up with something called cytokine release (a systemic inflammatory response), which is not a great thing; but you get the T-cell activation and different means of killing.



And so, again, bispecific antibodies, they're a novel immune therapy approach to bind antigens, which I call coatings on myeloma cells and these cytotoxic T cells. So those T cells, those T lymphocytes that are floating around in your body sort of saying, "Hey, do your job and kill some myeloma please."

So, there are different targets used, so this BCMA is one of the most commonly used one; but there are other targets, GPRC5D (G protein-coupled receptor, class C group 5 member D), and FcRH5 (Fc receptor-homolog 5) have shown interesting results and favorable safety profiles. These are typically IV. One or two are subcutaneous. They're given kind of frequently, and therapy goes on until progression. And again, we don't know exactly. None of them are approved yet, but I'm sure by the end of this year at least one will be. We don't know the order, when do you use it? These are being tested in heavily pretreated patients. They'll be moved closer to the front, but how does this compare to CAR T; and should it be used before or after? These are all questions that we don't have answers for at this moment.



THERAPEUTIC BISPECIFIC T-CELL ENGAGERS FOR MM

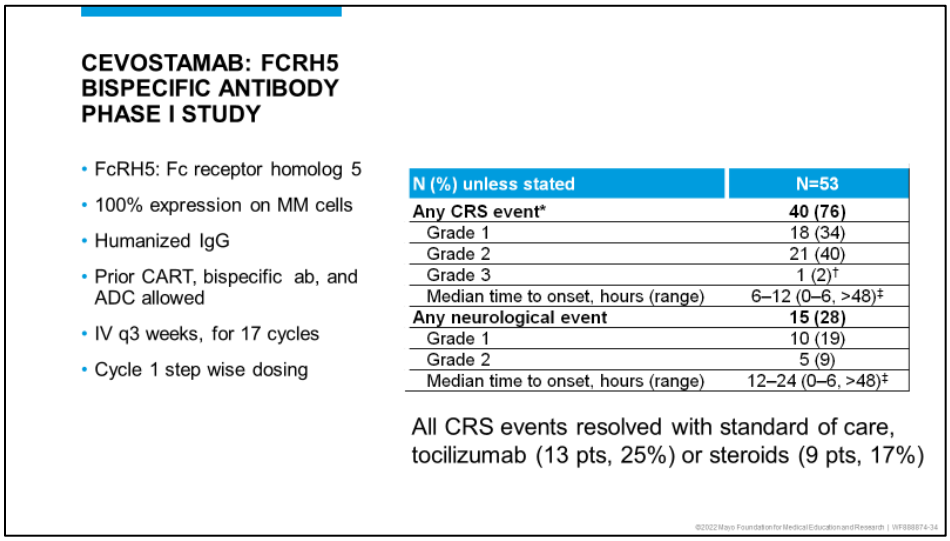
	Drug	Prior lines	ORR (%) @ therapeutic dose	≥ VGPR (%)	G3+ CRS (%)
BCMA / CD3	AMG-701	6	83	50	9
	TNB-33B	6	80	73	0
	REGN5458	5	62	NR	0
	Teclistamab (JNJ-64007957)	5	65	58	0
	Elranatamab (PF-06863135)	8	83	66	0
	CC-93269	5	89	33	3
	Talquetamab (GPRC5D/CD3)	6	70	60	2
	Cevostamab (FcRH5/CD3)	6	53 Not RP2D	32	2

Harison ASH 2020, abs 181; Rodriguez ASH 2020, abs 293; Madduri ASH 2020, abs 291;
Krishnan ASCO 2021; Bahlis ASCO 2021; Costa ASH 2019, abs 142; Berdeja ASCO 2021, abs 8008; Cohen ASH 2020

So busy, busy slide. What I'm showing you in the first column are the different BCMA targeting or the different bispecific T-cell engager drugs that are in studies. So the top six of them are targeting BCMA and CD3, which is just the T cell to bring it close. And then the bottom two are targeting something different, which is kind of nice because so many things are targeting BCMA. It's nice to have a different target as well. And then again, these are prior lines of therapy, so they're being studied in patients who've had five, six, eight prior lines of therapy.

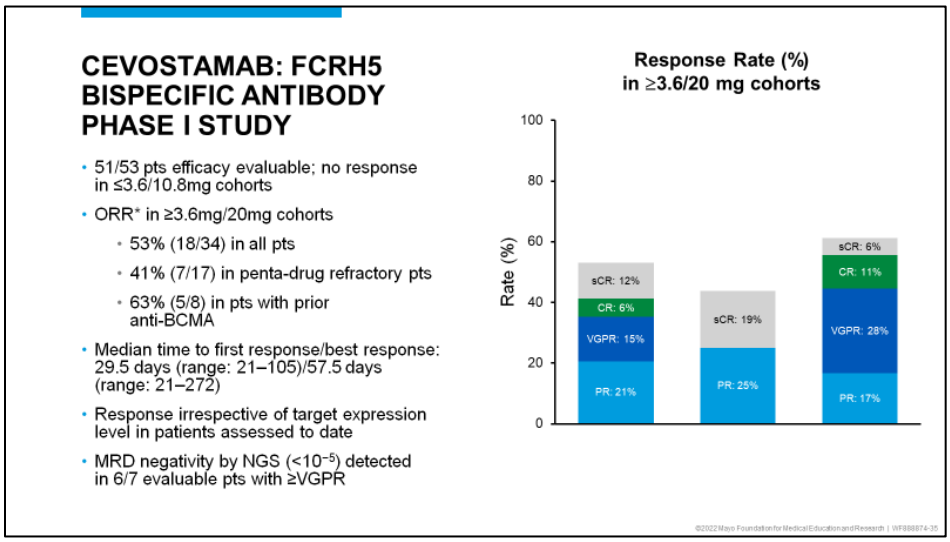
This next column in the middle is the overall response rate, so pretty darn impressive. Two-thirds to more than three-quarters of patients are responding to these medications; and deep responses, like what we call very good partial response in 50, 60, 70% of these patients.

Now what I have here in the final column is what's called cytokine release syndrome, grade 3, meaning patients are getting really pretty sick. Cytokine release syndrome is something where because we're engaging in activating these immune cells called T cells, patients can get very high fevers. They can get aches and rash and nausea and headache and diarrhea. Most of it is pretty mild and pretty easy to manage, but occasionally patients can get very, very sick as a side effect. And that tends to happen pretty soon, early on, within the first week or something of the infusion being given.



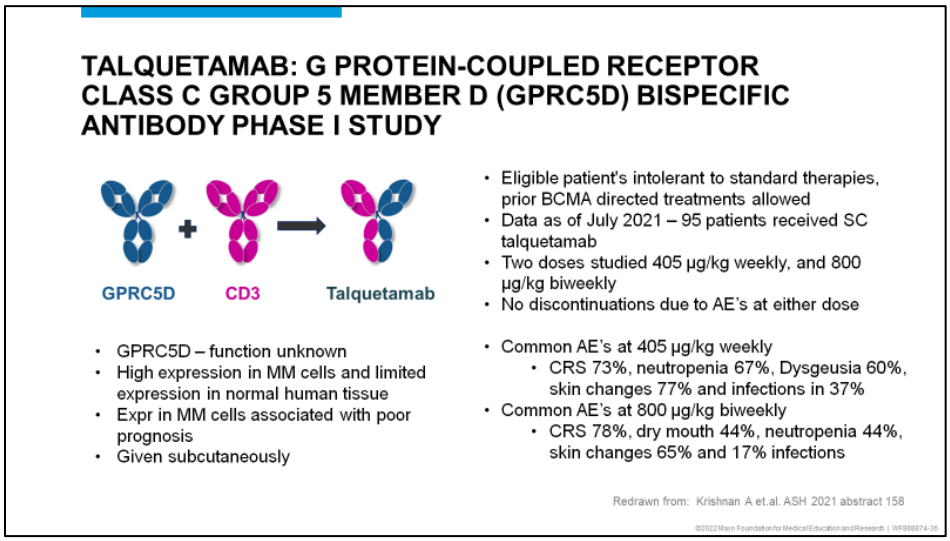
So here is, I'm just going to mention some of the, a couple of them. So, these are the cevostamab, which is using a different target. It was on that prior table. But just an example of, again, it's after the Fc receptor H homolog. (FcRH5) And you can see the CRS (cytokine release syndrome) here. So, any event is in three-quarters of patients or 76%, but most of it is a kind of a very low grade and only 2% is high grade. And it happens pretty early, within 6 to 12 hours of infusion.

Sometimes cytokine release can be very severe, and there can be even neurologic events. So, confusion and so that's something. But again, for with this agent, having severe neurologic events is not at all happening.

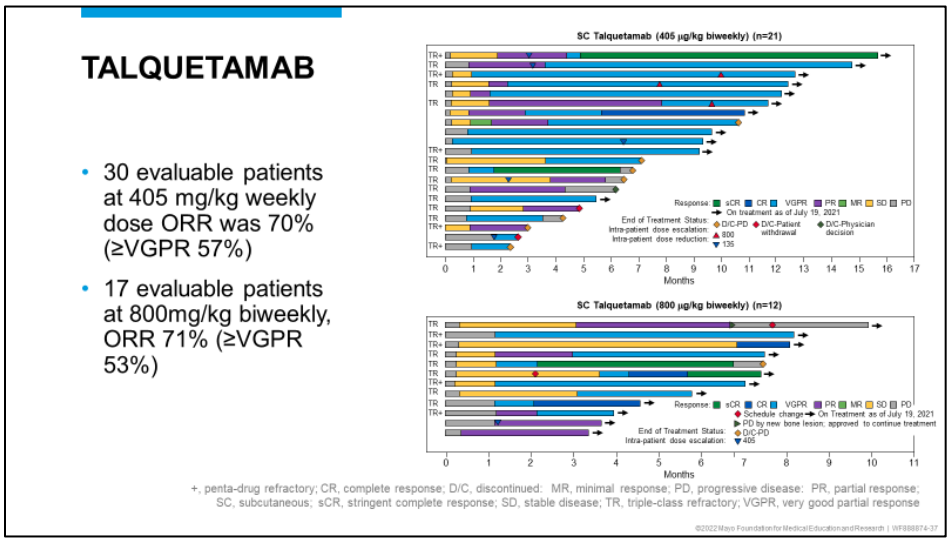


But again, just an example of showing what we look at in terms of response. So, this is 53 patients. Overall response is 53% having a response. If you break it down for patients who are refractory to five different drugs, five different classes of drugs, 41% responded and 63% of patients who had prior BCMA types of therapy responded.

And you can see that on the right-hand side is just the responses based on the dose levels, the different cohorts, and the dose levels given to the patients.

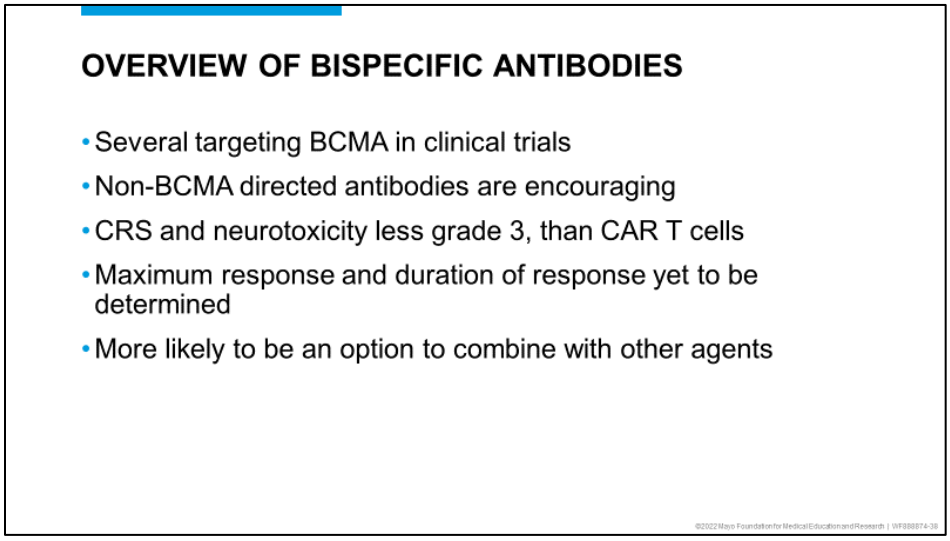


In terms of the other, the talquetamab, again different target from BCMA. So, these are interesting because they're just so different. Again, a cartoon that it's sort of this, you're binding both CD3 in pink and the coating on the myeloma cells called the GPRC5D, this is in phase I studies. The most common types of side effects, there can be kind of rashes and skin changes, is sort of one of the side effects that's unique there. But people can have low counts and funny taste in their mouth, a dry mouth, and so forth. But again, these are just exciting things that are in clinical trials.

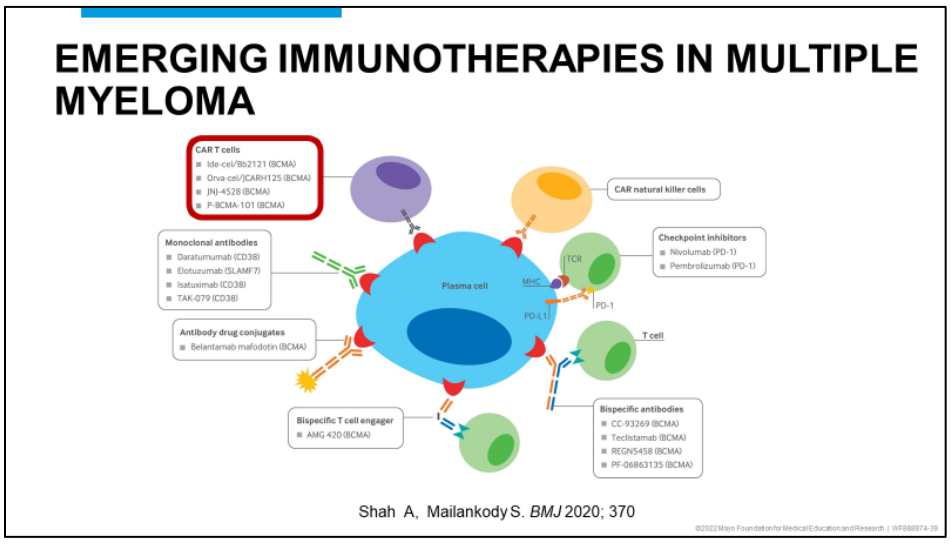


And, again here, you can again see what we call these swimmer's plots, each going across ways, like each row is a separate patient; and the color coding is showing you the depth of response of green as a stringent complete response and the light blue is a very good partial response. And then you have the months along the X axis, and you see that these, the patients are going strong at a year, many of them. There's some patients that had shorter responses, and the upper panel is showing one

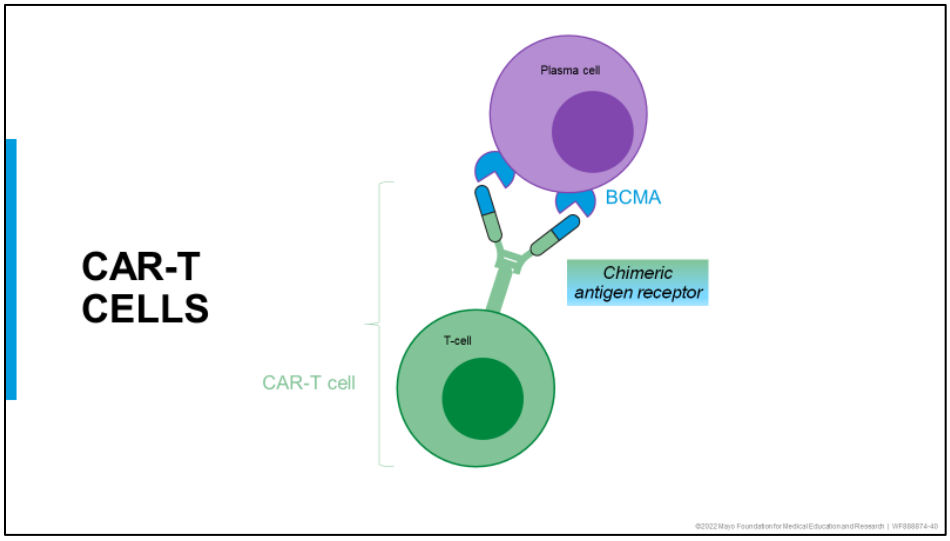
particular dose, the 405 microgram; and then the lower panel is showing higher doses because, again, these are dose escalation types of trials. And you can see that more patients have ongoing benefit, as represented by the little black arrow.



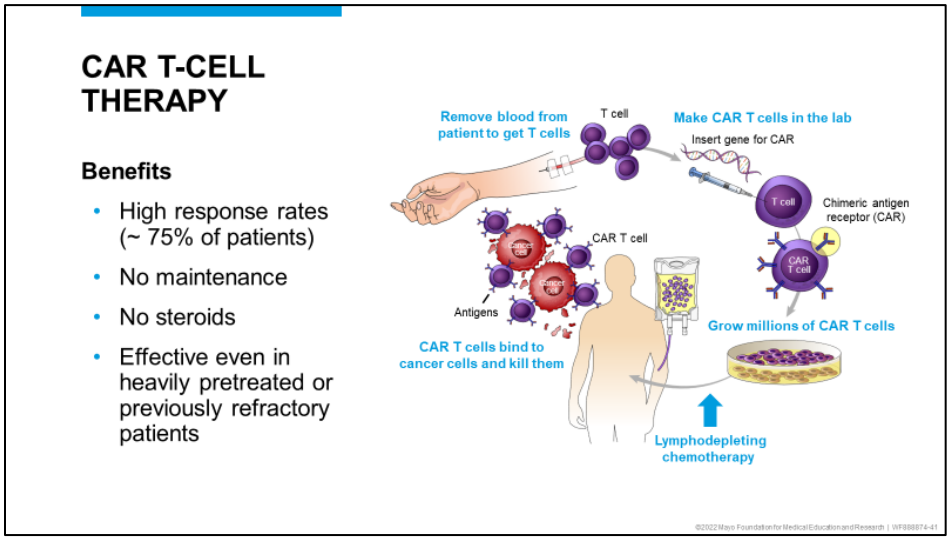
So more to come. So, what can we say about bispecific antibodies? I didn't go into detail about the BCMA ones, but it was in that table. But there are a lot in clinical trials, and I suspect this year at least one of them will be approved. And then I gave you a little bit more information about the non-BCMA, the alternate pathway, are also encouraging. There can be toxicity, so these are often given at the hospital; and you need to be observed and so forth. But we don't even know the duration of response. The data are too immature because people are still doing well. And so, what's the endpoint? What's the average going to be? That is a work in progress. And then they may combine with other agents at some point.



So, then finally, moving to CAR T cells, and two of these are now FDA approved, so ide-cel (idecabtagene vicleucel/Abecma®) and cilta-cel (ciltacabtagene autoleucel/Carvykti™) are both approved, so two are there. And so, let's talk about that.



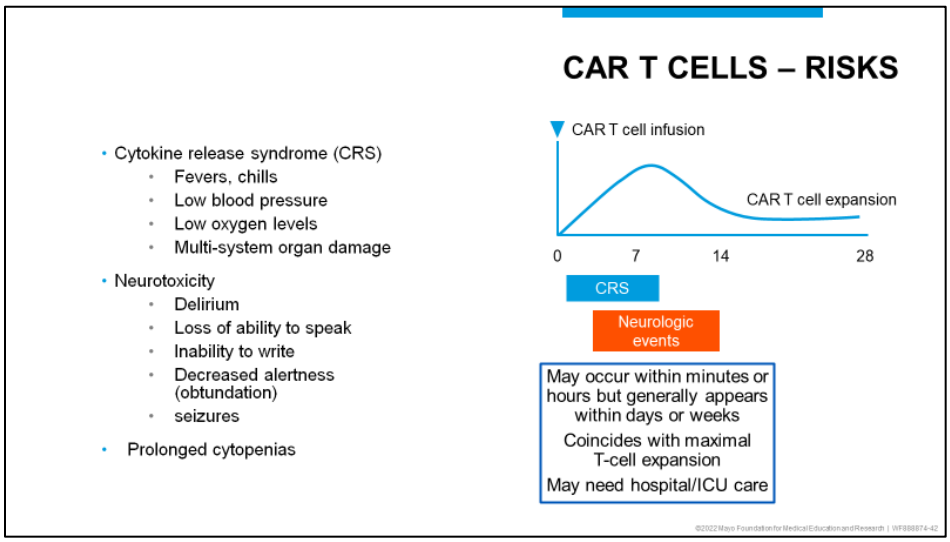
So, here's the CAR T. So, this is different. Here's the myeloma cell or plasma cell in pink up at the top, and here in blue are sort of the, most of them are targeting BCMA, so that's the coating that we're attacking, those blue little PAC-MEN that are attached there. And then what we do for CAR T cells is we take patients' T cells from their body, and I'll show you a cartoon in a moment, and we modify it and grow it up and then give it back as a transfusion to the patient. And so, it has this what we call chimeric antigen receptor, that's the CAR in CAR T cell, that then hopefully now has primed your T cell and targeted your T cell against the myeloma cell.



And so, here this is the nuts and bolts of the mechanics of how it's done. So, we have to remove the T cells from the patient, and that's done by a method called leukapheresis, similar to the procedure if you had stem cells collected, it's the same machine just different settings and shorter sessions

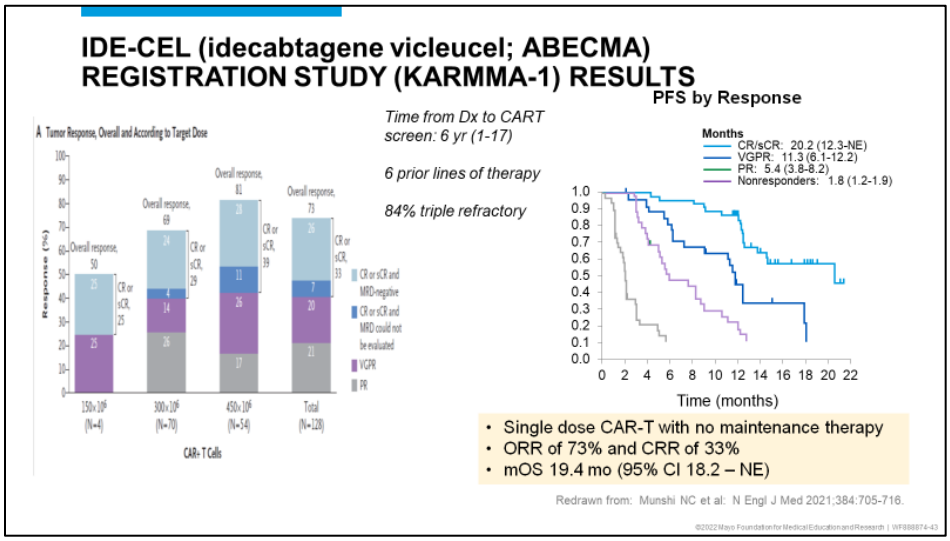
typically. But we remove those T cells and then they go to the lab where they're modified, so a gene for the CAR is inserted, and then these cells are grown up. And then they basically come back and can be infused or transfused to the patient. And then the goal here is that they recognize myeloma and kill the myeloma.

High response rate. So, about three-quarters of patients respond. Nice thing is currently there's no maintenance, but down the road, who knows, there may be. But it's sort of a one-shot deal. There's no steroids. Everybody hates their dexamethasone, and it seems like every program has dexamethasone, so that's not a part of it. And it appears to be effective in heavily pretreated patients.



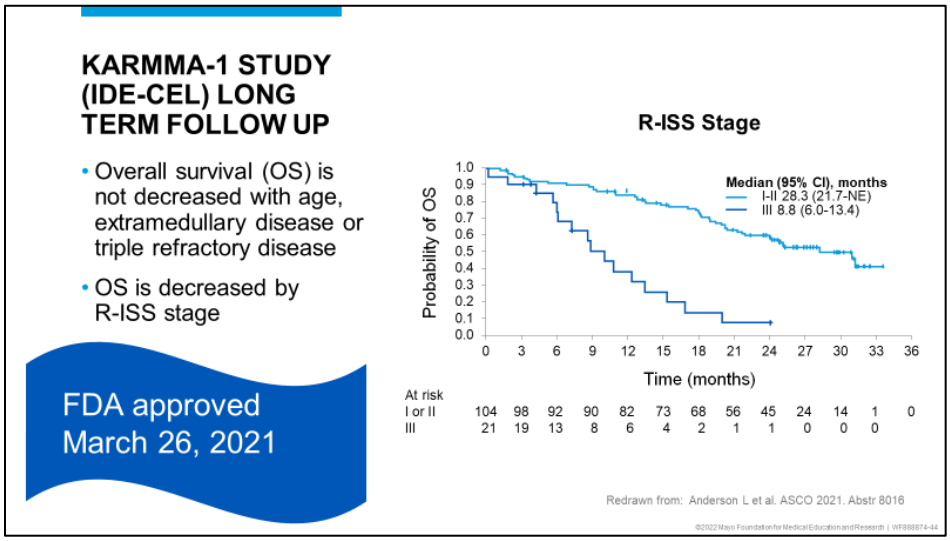
Again, the cytokine release, I told you, is something that can occur. More common it happens with the CAR T than with the T-cell engagers. And so, I mentioned fevers, chills; I didn't mention the low blood pressure, low oxygen. With the CAR T, there can be even multisystem organ damage, but we're getting much better at managing that giving drugs like tocilizumab (Actemra®) and such. So, it's less of an issue than it had been, but there can be neurotoxicity, including delirium and really some inability to speak and talk and confusion, rarely seizures. Again, we're much better at managing this than we had when these were new agents.

So, this little blue curve thing here essentially times zero is when the patient gets their CAR Ts infused to them or transfused, and then typically the cytokine release is going to happen within usually the first week, the neurologic events within the first kind of week or two and that's why patients are hospitalized for these and monitored.

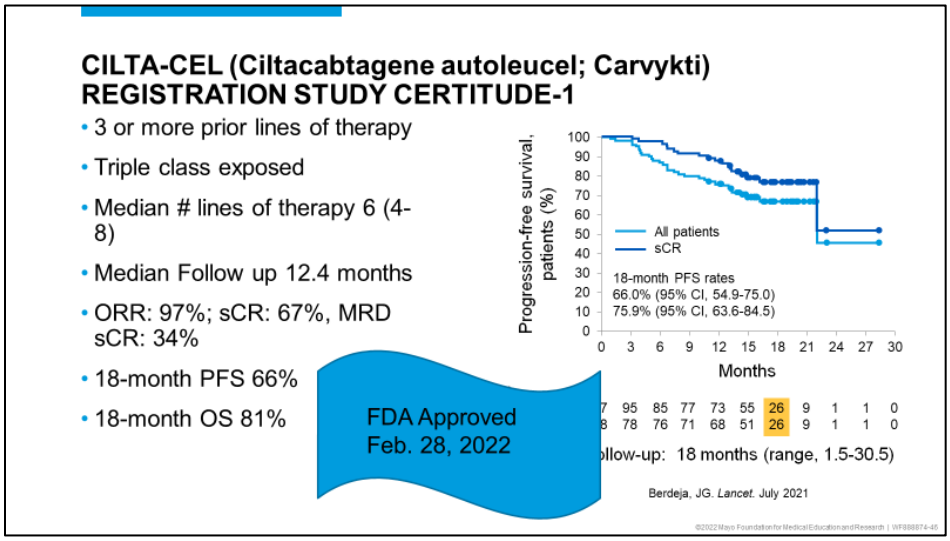


So, what about some of the specifics? So, ide-cel, (idecabtagene vicleucel) also known Abecma™, this is the registration study. These patients were heavily pretreated six years into their diagnosis, on average six prior lines. 84% were triple refractory, meaning refractory to proteasome inhibitors like Velcade and like Revlimid, pomalidomide, that group and, also, antibodies like daratumumab or isatuximab.

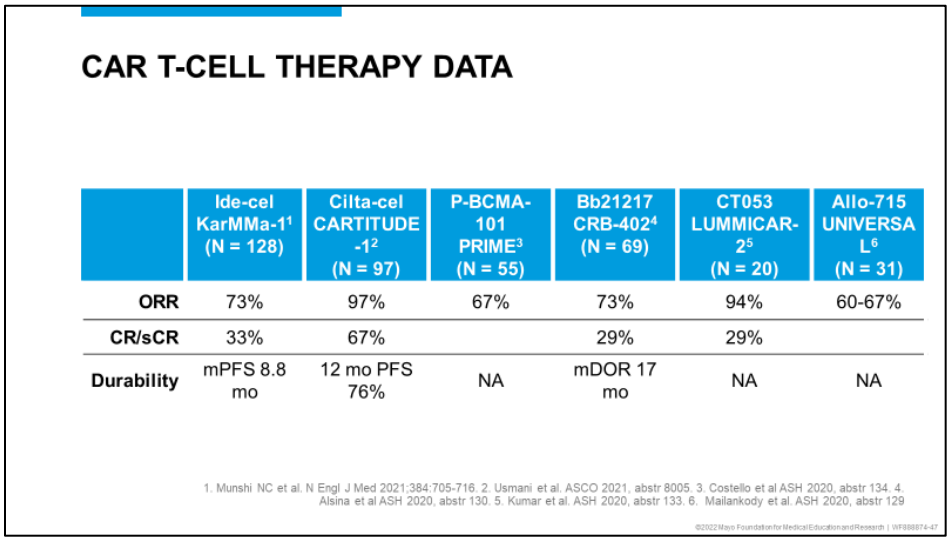
And this is the tumor response. So, what this plot is showing, so this is different dose levels. Each of the bars represents a different dose level. And so, they start with a low dose is the left most bar, and then they increase the dose the number of cells given. So, there's the 300 x 10^6 and then the third bar over is showing 450 x 10^6 and then just all of the patients together. And so, here you can see at the highest dose level the overall response rate is basically 81%. And so, the light blue is complete response or stringent complete response (stringent CR) and MRD (minimal residual disease) negative, the dark blue is just CR or stringent CR. So, CR or better in 39% of patients, very good partial response in 26% of patients and a partial response in 17%. And then what you can see here is the progression-free survival. So, again, the blue, the top blue light blue are those patients who had the CR or the MRD negative CR. Actually, I'm sorry, it's just the CR. And those patients the time to their needing new therapy or time to progression was on average 20 months. The dark blue is the very good partial response, so on average, time to needing a new therapy or progression is about 11 months. And, again, you can see if you didn't have as deep a response, the time of benefit was less, at five months for the partial response people and non-responders needed therapy sooner. And so, single dose overall, as we said, 73% response and survival, for all-comers, in these very heavily pretreated patients, was just under two years or over a year and a half.



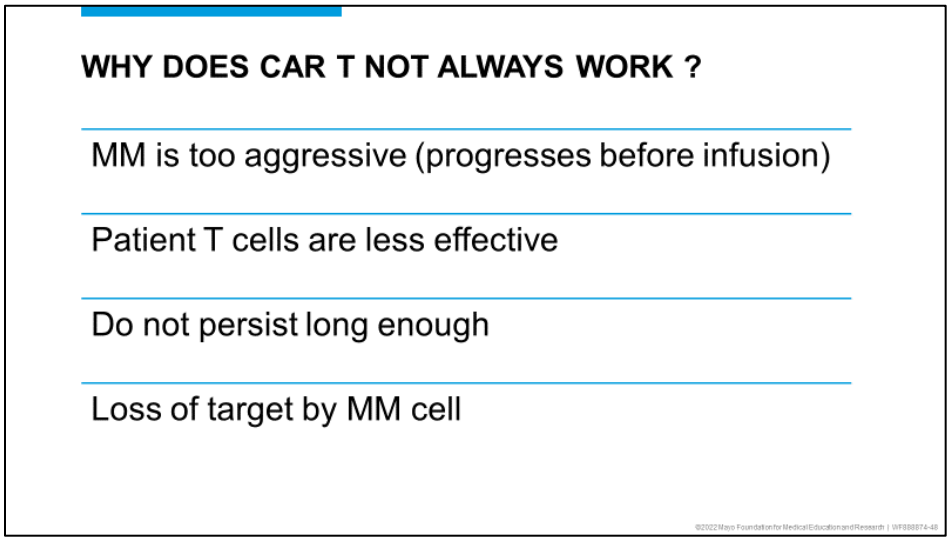
This next drug, which was just recently approved, is the- Oh what did I have here? I'm sorry, so here we have, I'm sorry, this is the KarMMa-1, the ide-cel, and it was approved in just last year. And you can see the survival based on the staging here, so the lower stage the better in terms of overall survival. And, again, this was FDA approved about a year ago.



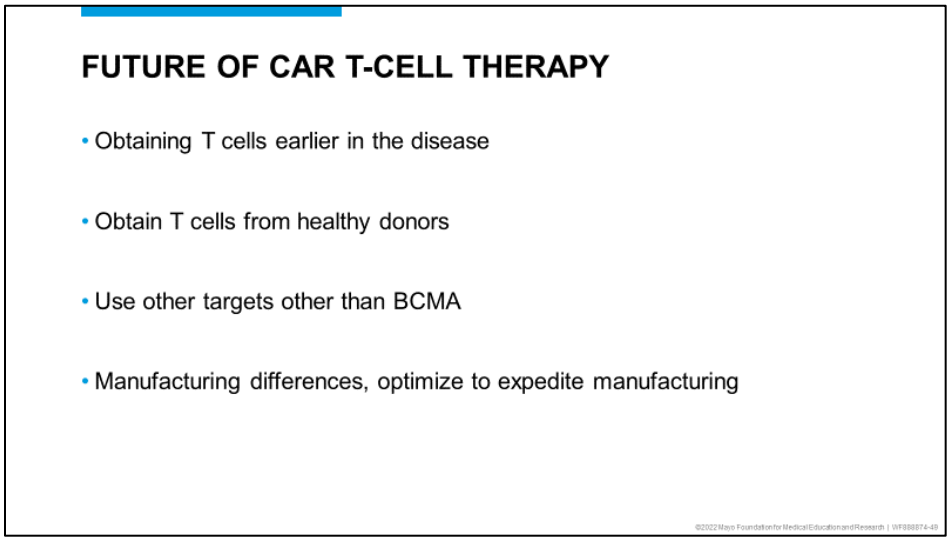
And the next drug is the cilta-cel, or also known as Carvykti™, and this is the registration trial that got it to approval. And you can see the time on the right, the time to progression or progression-free survival really looks excellent. Sort of 80% progression free if you were in CR, but even those patients who had less than a CR, 18-month progression-free survival was about almost 70%. And so more to follow, but it looks very, very promising as well. And that was just approved a few weeks ago.



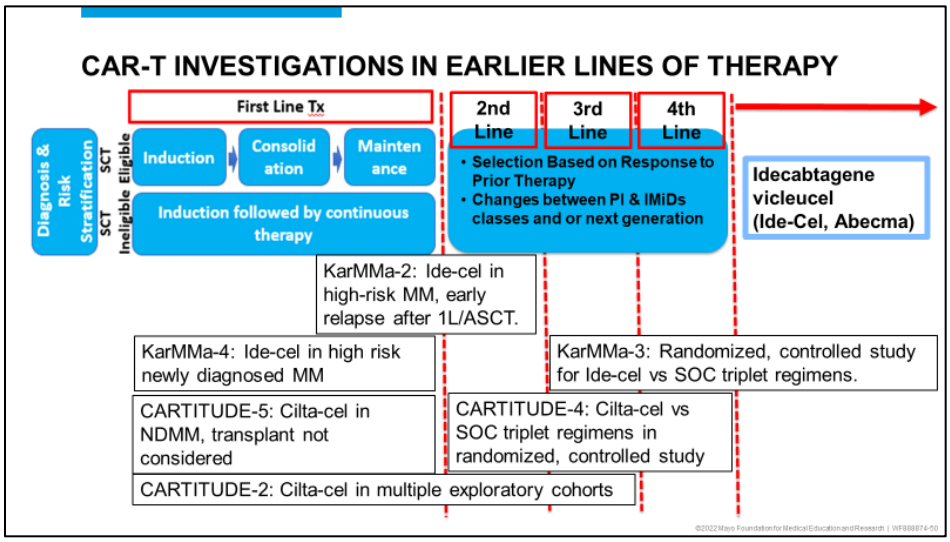
So, this is to the ide-cel and the cilta-cel are the left two most. And you can see response rates and the CR rates and the progression rates that are described. I can't tell you that one is truly better than the other because this is what we call a cross-trial comparison and so, again, the patient populations may be different and so on and so forth. I think they're both major advances. And then to the right there are other products that are in trial and being looked at. And so, you can see the response rates are also very good. So, lots of research and work and study in this space.



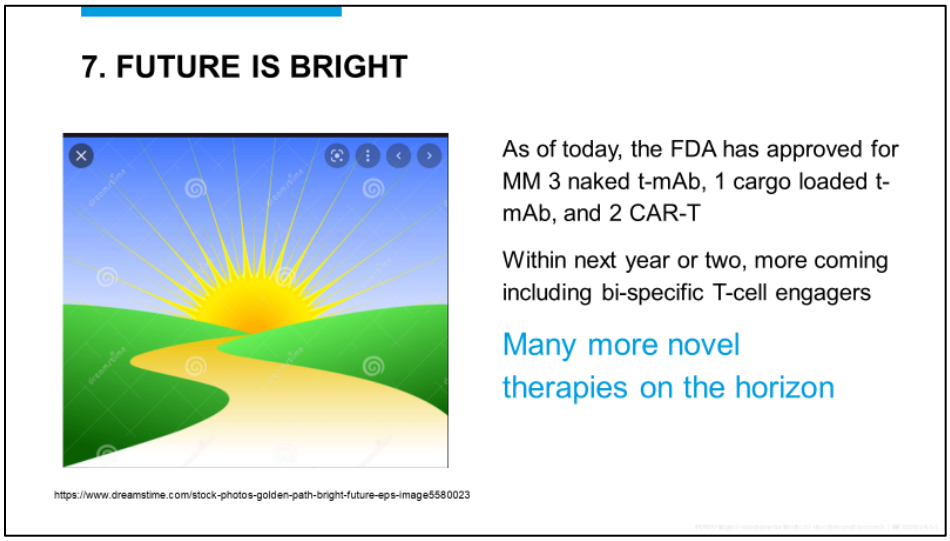
And so why does it not always work? Well, sometimes the myeloma is too aggressive. It even progresses before you get your infusion. The T cells just don't seem to want to do the job even if you try to train them. The T cells may disappear too fast and so don't get enough time to do the killing of the myeloma or the target that it's against may be lost.



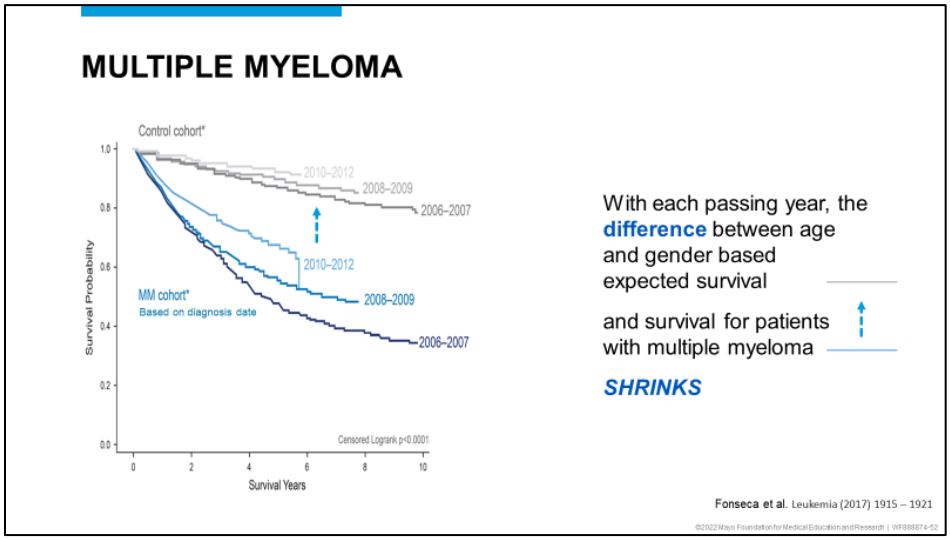
And so the future there's looking at getting the T cells earlier in the disease before they've been beaten up and so forth. There's a strategy in research looking at using T cells from healthy donors. Also, work looking all of the two CAR T that are approved are targeting BCMA but maybe would be a CAR T targeting CD38 or other things may be of use since all these strategies are all being looked at. And then there are issues with manufacturing. It is a long wait and there are lags in timelines, and it can be very frustrating, especially with the clinical trials. And then I think with COVID (coronavirus disease 2019) too, things got slowed down.



And so, this is a really busy slide, but the whole point is that there are CAR T studies that are being moved into sort of early first line treatment, second line, third line, fourth line. And here a number of different clinical trials really investigating using them earlier on, because the approvals for these drugs are really after third-line therapy, so we need to show that it's safe and effective in an earlier line, so a lot of work being done.

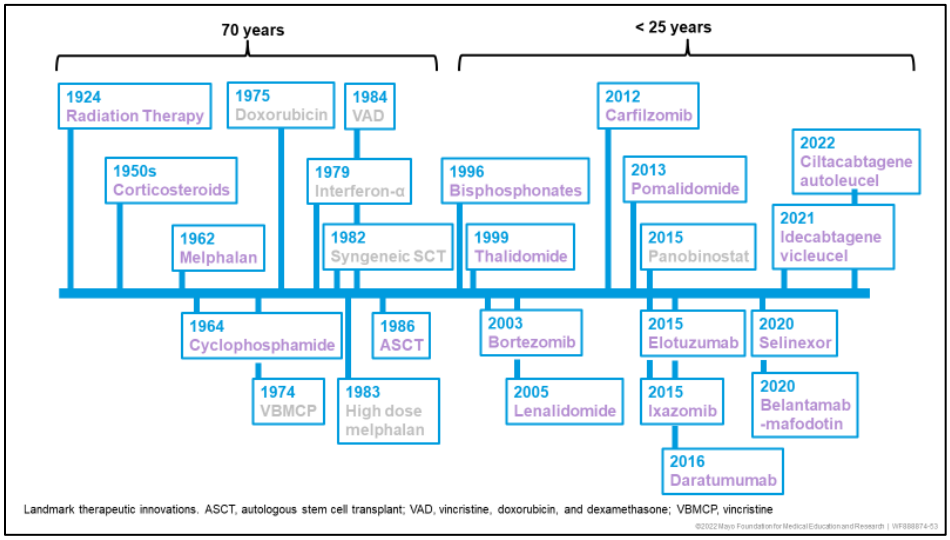


So, the future is really bright. As of today, in the immunotherapy space, FDA has approved, for multiple myeloma, the three naked therapeutic monoclonal antibodies, one cargo loaded or antibody drug conjugate, T-cell monoclonal antibody and two CAR T. Within the next year or two, we're going to have more, including the bispecific T-cell engagers and just more and more novel therapies on the horizon.

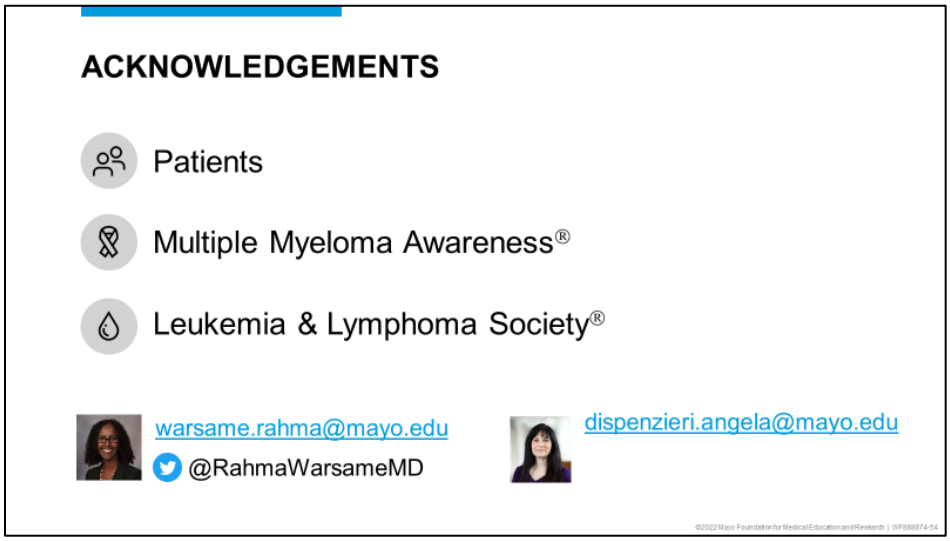


And a couple of last words. Here is what we call a survival curve. These are old data in terms of — because the last look is patients diagnosed in 2012 — and so we're ten years hence from there. But what the gray curves are showing is what age-matched people you'd expect them to live not with myeloma. Just regular people without this diagnosis. And survival is getting better for everybody. We're doing better in all kinds of healthcare and so forth. And so, depending on the diagnosis date in gray, this is the expected – or not diagnosis but just sort of benchmarking it to people in that period what their expected survival is. What the blue lines are is survival by year of diagnosis of myeloma. And so, people who were diagnosed in 2006, their survival was not as, quote, "high" as the survival

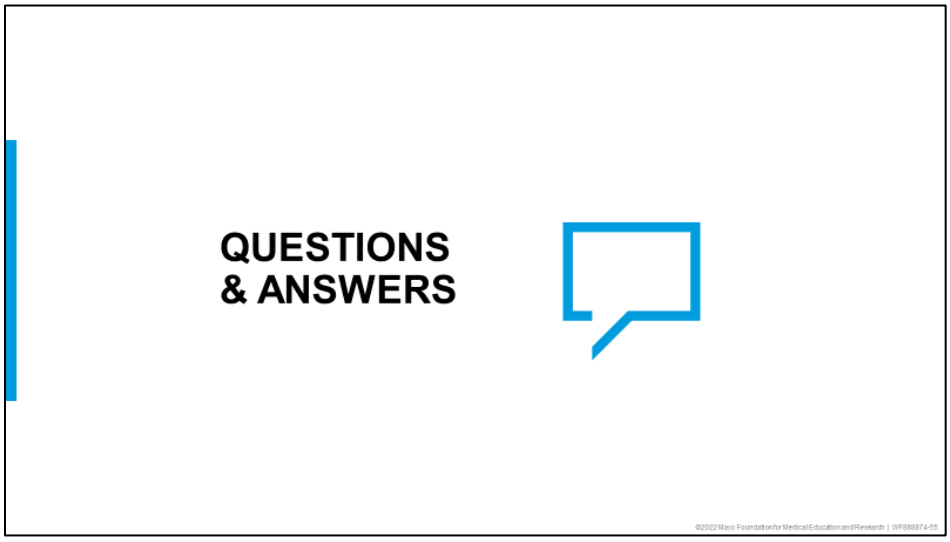
of people that were diagnosed just a couple of years later, as compared to people diagnosed just a couple years later. And so, what is that going to look like for people who are diagnosed in 2022? The idea is to get the blue lines to be as good as the gray lines to really improve the survival for patients. And we are getting better. We are moving the curves upward for patients.



And part of the reason, busy, busy slide, but what this is, is sort of a timeline not to scale. On the left, you have 70 years of treatments for myeloma, 1924 up through the '90s. And basically, there were really radiation and corticosteroids, melphalan (Alkeran®), cyclophosphamide (Cytoxan®), some combinations, transplant, auto (autologous) transplant started being done. But the stuff in gray really were not major hits. They sort of came and went. In 70 years, that was the progress. The lavendery color is really the big progress. Now if you look at the last 25 years or less than 25 years, look at all the different lavenders that we have. We have so many more drugs available to patients. And so really exciting time, hopeful time.



And with that, I want to acknowledge Dr. Warsame. She started the slide deck, and I just made a few little tweaks here and there and just, obviously, all of you and families and everybody who does research to really move this forward and The Leukemia & Lymphoma Society, etc. And happy to take questions.



Lizette Figueroa-Rivera, MA

Well thank you so much, Dr. Dispenzieri. It's great that you were able to provide such a wealth of knowledge in regard to myeloma and your last slide really showing the advancement in the last couple of years. It's great to see.

QUESTION-AND-ANSWER SESSION

Lizette Figueroa-Rivera, MA

It's now time for our telephone and answer portion of our program.

(Operator Instructions)

Lizette Figueroa-Rivera, MA

Thank you. And doctor, we'll take the first question from Lori. Lori is asking, "How do you know what particular protein a myeloma cell is expressing so that you know how to target it with a particular immune therapy?"

Angela Dispenzieri, MD

Yeah, that's a great question. So, some of these things are so ubiquitous, like just they're there. CD38 is virtually on all of these, almost all myeloma cells. Over time, if you use a lot of anti-CD38 antibody or whatever, that might go away, and one can do immunohistochemistry to look at that. And the same thing, BCMA is really just it is expressed a lot on myeloma cells and virtually all myeloma cells but with additional therapy, that might kind of go away.

When these drugs were started, we used to do more immunostains to see if it was expressed and so on and so forth and, certainly, it's part a lot of these trials to see, but we're learning more and more, at least in our first go around targeting one of these coatings or antigens, that you don't necessarily have to test. But I think as we use more things targeting a same epitope, we may need to do more staining. So, it's more a research thing than a standard thing. So, the short answer is usually you don't have to check for at least the things that are FDA approved, but that may change. But it's typically it would be stains on the bone marrow.

Lizette Figueroa-Rivera, MA

Thank you, doctor. And we'll take the next question from the telephone audience please.
Operator

Thank you. This question comes from Mark calling in from California. Please go ahead.

Mark from California

Yes. What is done after relapse from CAR T?

Angela Dispenzieri, MD

Right. So, it depends on a couple of things. Number one, it depends on when the CAR T is given and what a person has had. So, for a lot of the original trials, it was kind of used as almost everything was used up, so to speak, and there was very little to use after. As these are FDA approved and it's moved further upline, then you kind of look and say, "Okay, what hasn't the patient had?" There may be things that have been approved or maybe even in clinical trials that you could use or different combinations that you hadn't quite used that you would go to. So, it really depends on what came before CAR T. A lot of the like the bispecific antibody trials they exclude patients who've had prior CAR T, but there are more and more now that are allowing prior CAR T, so conceivably a bispecific could be used. So, the short answer is it depends on what you had before and what hasn't been used up before.

Lizette Figueroa-Rivera, MA

Thank you for the question. And our next question is coming from Eileen. She's asking, "Can you do a second autologous stem cell transplant years apart from the first one?"

Angela Dispenzieri, MD

Yes. Absolutely. We definitely, in younger people especially, we collect enough for two transplants with that in mind. If a patient has had a really long remission – five, ten years or something – with the first transplant, it's so appealing to say, "Hey, should we give it another shot because maybe I won't get the same duration I got previously, but even if I have four years or something without having to do all kinds of other therapies, that is still an option." I think though with all these other new therapies too, people are like, "Well, gee, should we use a CAR T first instead of the second transplant?" So, there are just a lot of options and so it gets very complicated. But it is definitely a viable option. I mean certainly if somebody relapses two years after their first autologous transplant, the thought of doing a transplant right after that is not that appealing because you know the duration of response will be a little bit shorter yet than that. So, there are so many other good things to use.

Lizette Figueroa-Rivera, MA

Thank you. And we'll take the next question from our telephone audience please.

Operator

Our next question comes from Barb calling in from Pennsylvania. Please go ahead.

Barb from Pennsylvania

I was wondering what the difference is between the Darzalex infusion and the Darzalex shot. What are the side effects?

Angela Dispenzieri, MD

Yeah. So daratumumab, Darzalex, can come as a subcutaneous injection which was more recently approved or the intravenous. The subcutaneous is really very much more convenient because there's less sitting in the chair time for the patient and so many people really prefer that. The side effect profile, the infusion reaction rates are a teeny bit less as well, but really the biggest advantage is the chair time. And because especially the first eight weeks it's a weekly administration and so, spending several hours in an office getting chemotherapy is not anybody's idea of a good time. And then the next 16 weeks, it's every other week. And so, the subcutaneous is definitely more convenient. In terms of efficacy, it really appears to be quite similar and as far as side effects, maybe a little bit less with the subcutaneous.

Lizette Figueroa-Rivera, MA

Thank you for the question. Our next question is from Tom. Tom is asking, "Is it common with myeloma to experience pain that feels like it's coming from deep in the bones? Does that signify bone lesions?"

Angela Dispenzieri, MD

Yeah. So, it can, yes. It can signify an active marrow. Sometimes doctors, though, too they'll give shots to stimulate the white count, something like Neupogen® (filgrastim) or Neulasta® (pegfilgrastim) or G-CSF (granulocyte colony stimulating factor), and that can cause some bone pain too, but sort of that deep pain could definitely be myeloma growth. But there are all kinds of other aches and pains that people have, so it's not like it's a guarantee, but in the right setting it certainly could be. And if a person has that kind of aching deep inside the bone like that, more than likely it's going to be pretty evident on the bloodwork that things are moving along.

Now if you do x-rays too and you would potentially see a lesion there too. So, again, the rule is if you have bone pain in a patient with myeloma, you should definitely do imaging to make sure it's not something. And if there's not something there, sometimes patients with very advanced disease, where the myeloma is very proliferative, can get overt diffuse bone pain. But if it's localized, it's worth an image to make sure that it's not something important.

Lizette Figueroa-Rivera, MA

Thank you. And our next question from Carolyn. Carolyn is asking, "How do you define remission?"

Angela Dispenzieri, MD

Yeah. That's a really, really good question. So, remission in the truest sense is when there's no evidence, for example, by minimal residual disease testing of myeloma, that is the sort of the truest sense of remission. I think we use it often if somebody's in a CR or even almost a complete response, people may also sort of call that a remission. I mean in the purest sense, it should be MRD negative, no evidence of disease at all. But I think sometimes we get a little loose with the expression. But, yeah.

Lizette Figueroa-Rivera, MA

Sure. And there are a lot of folks asking if myeloma is curable at this point; and if it isn't, when do you project that it will be?

Angela Dispenzieri, MD

Yeah. That's a great question. I wish I knew the answer. There are patients throughout the eons, I mean I've been in this business for 25 years and I have patients that are in remission after their transplant at 20, 25 years later, which is extraordinary, and they didn't even get any of the fancy-smanshy stuff. They just had like old-fashioned chemotherapy with a transplant. And as I'm following a patient 20 years and they're still in remission, do I say they're cured? I don't even have the courage to say that. So even back in the dark ages, so to speak, of myeloma therapy, there are patients here and there who do exceptionally well and are in remission, and you sort of go, "Hmm, is that a cure?"

In terms of the modern day and with the newer therapies and things, it's really hard to know what's good enough to call it a cure. Certainly, if there's no evidence of disease, MRD negative for five, ten years, do you call it at ten years that that's a cure? I guess it depends on who you are. It's just so hard to know. Even like I don't do breast cancer anymore, but I remember there were patients who relapsed 20 years after their original diagnosis and you would have thought they were cured, so to speak, and here they are. And so, cure is a funny word. But I think I would certainly say that there are patients historically and more so now that have enduring remissions and enduring times and even not even an MRD negative one but even in old-fashioned complete response that can do well for so long. And because we have better therapies, we see more of those patients. But, yeah, when do you sort of throw down the glove and say, "We've cured X number of people"? I don't actually have a good answer for that. But I'd like to say that the majority of patients are in sustained remission for ten years or so. That would be really great, and somebody might call that a cure, somebody else might not.

Lizette Figueroa-Rivera, MA

Right. Thank you. And for some of our folks, can you just go over what MRD means?

Angela Dispenzieri, MD

Yeah. So MRD is an expression, minimal residual disease, or measurable residual disease. Sometimes people use them differently. But the idea is that depending on how carefully you look, and not to say that anybody's careless, but it's really the technology, your ability to really, really look in the bone marrow deeply to find one in 10,000 cells are myeloma cells, one in 100,000 cells are myeloma cells, one in a million cells are myeloma cells. That ability to really look that carefully or detect that few cells or one in 10 million, that is MRD. So, we used to call MRD it was one in 10,000. If we couldn't find a myeloma cell, if we looked at 10,000 cells from the bone marrow and we couldn't find one myeloma cell, we'd call that MRD negative; there was no evidence of myeloma. But then when we got better technology and we were able to look at one in 100,000, we're like, "Oops, the ones we said that had no disease, there actually was; we just couldn't count, or we couldn't see it." And so, the deeper we go, probably the closer we are to understanding the likelihood of cure on some level. And so, it is a measure that it can be done on the bone marrow. And, again, some of our therapies have higher rates of MRD. When we talk about it, it's always important to define how we're calling the MRD, how carefully did we look when we said there was no measurable disease and the acknowledgement that, in general, the deeper the response probably the better the outlook certainly for populations. But each patient is very different and there are patients who may still have a residual small protein and will just kind of be stable for years and years on end.

Lizette Figueroa-Rivera, MA

Thank you for that explanation. And we'll take the next question from our telephone audience please.

Operator

This question comes from Charles calling from Connecticut. Please go ahead.

Charles from Connecticut

Hi. I want to know; I've been off of chemo for six years and it's starting to show traces again. And with the new therapies, what do you recommend that doesn't give you neuropathy? I got neuropathy in my feet from Revlimid.

Angela Dispenzieri, MD

You got it from Revlimid, okay. Well, again, yeah, neuropathy is a bugger. So, the anti-CD38 antibodies daratumumab or isatuximab I think is definitely going to be part of a treatment program for many. So, usually people are giving three drugs, we call it a triplet, right. Dex is, of course, one of them just to everybody's chagrin, and then often a CD38 antibody like daratumumab or isatuximab and then the partner there would be if you relapsed on Revlimid, it would be, if you were actually relapsing on Revlimid if it was with maintenance, then either pomalidomide with the daratumumab or

carfilzomib with the daratumumab or even carfilzomib-pomalidomide and dexamethasone are probably the most common. And those should be pretty good in terms of neuropathy. And, of course, there might be some clinical trials that might be of interest that have some of these active agents and that don't really cause neuropathy either.

Lizette Figueroa-Rivera, MA

Thank you. And along those lines, we do have a lot of folks asking about neuropathy and if there's anything that could be done for the neuropathy.

Angela Dispenzieri, MD

Yeah, yeah. So, the best thing for neuropathy is trying to be very frank with your doctor when you're getting the symptoms. Sometimes I think patients are afraid to say that they're having symptoms because they don't want to reduce their medicine and they want to be brave and tough. So, really important to be honest with your doctor about your side effects. So, that's number one. But once the neuropathy is there, there are a number of different medications that can be used.

The most common medicines that are used are in the antiseizure class of drugs like gabapentin (various brands) or pregabalin (Lyrica®), also the antidepressant class like Cymbalta® (duloxetine) or even some of the old-fashioned things like nortriptyline (antidepressant, various brands) and amitriptyline (antidepressant, various brands). Sometimes topical lidocaine (local anesthetic) or compounded lidocaine preparations can help. There are different sort of therapies, something like scrambler therapy, which is kind of an electronic device that sort of tries to retrain nerves. Sometimes people say acupuncture can help. There are supplements. Some people take supplements, B vitamins. It's unclear that they really truly help. You don't want to overdose on vitamin B6 either. Alpha-lipoic acid (an organic compound with antioxidant properties) is used for diabetic neuropathy and so some people take that. Unclear in the myeloma neuropathy drug space whether that has truly helped or not. If it's really significant, working with a pain specialist can also be of value.

Lizette Figueroa-Rivera, MA

Thank you so much. And the next question comes from Michael and Jack, "Do you think CAR T treatments will replace stem cell transplants in the future?"

Angela Dispenzieri, MD

It's a fantastic question, and I don't have an answer. It's interesting. In the lymphoma space, they're further ahead than the myeloma space. There are randomized trials asking that exact question. So, actually, even in the myeloma space, there are trials looking at that. So, I don't know. It may not be an either/or, but I think for sure that question needs to be answered.

Lizette Figueroa-Rivera, MA

Thank you. And we'll take the next question from our telephone audience please.

Operator

This question comes from Deborah calling from Texas. Please go ahead.

Deborah from Texas

Hi. I was diagnosed in 2010. 2014 went through several treatments. 2014 had a stem cell transplant, and I was good for five years. And that stuff grows fingernails like dog fingernails. And I relapsed. I was on Revlimid, allergic to that. And now I'm on Pomalyst® and Darza (Darzalex®/daratumumab), and the last three PET (positron emission tomography) scans were clear. And my last lab work all of the light chain numbers were normal. At what point do I stop treatment?

Angela Dispenzieri, MD

You're not going to like my answer. I mean that's wonderful news, but we tend to keep staying on therapy. We get afraid to stop. It's always a very personal decision-making process that goes on with the patient and the doctor. These days, it's kind of like we just keep at it. We're afraid to stop with the maintenance. But if there's side effects and things or whether it's a financial burden or you name it, between the physician and the patient and often the patient's family, that conversation happens. And it's really a very individualized decision, but, in general, if somebody's on pomalidomide in the relapsed setting, typically people are staying on it until it stops working.

Lizette Figueroa-Rivera, MA

Thank you. And the next question comes from Tamra is asking, "Why is myeloma more prevalent in the African American community? Can it be specific to genetic history, for example, sickle cell anemia?"

Angela Dispenzieri, MD

Yeah. So, really great question. So, don't think it has anything to do with sickle cell anemia, but I think a teeny bit there are certain what we call polymorphisms (a common change in the genetic code in DNA) that might be a little bit more prevalent in African Americans, but it doesn't fully explain it. I think we really don't know the answer. We know that the condition, the premalignant condition called MGUS, or monoclonal gammopathy of undetermined significance, is also more prevalent in African American people. So, if you have more of the premalignant stuff, it makes sense that you have more of the malignant stuff or the cancer stuff, but it pushes the question back, why do they have more of that premalignant thing and how much of it is genetic? We just don't fully understand, but to the best of my knowledge, it's not related to sickle cell. I see a lot of myeloma, and I don't see many patients with sickle cell and myeloma. But it is an important question. And if we understand that better, it may help African Americans, but also it may help other myeloma patients too, in terms of is there a difference. Because we don't really understand myeloma. There's a lot that we know about how to treat and this, that and we can prognosticate, but, like, why does anybody get this stupid disease, really, we can't give you that answer. And so, if we could have that answer for any population, that would be fantastic because that would really help us understand this disease.

Lizette Figueroa-Rivera, MA

Thank you. And our next question is from Stuart. Stuart is asking, "Is there any news from trials or treatments for people with myeloma and amyloidosis?"

Angela Dispenzieri, MD

Yeah. So, I treat a lot of amyloid. For most patients who have myeloma and amyloid, the disease is more about the amyloid than the myeloma in the sense that the things that ail amyloid patients, the symptoms that ail amyloid patients, are different than what ail myeloma patients. So, a symptomatic myeloma patient is going to report bone pain and fatigue as the most common things, whereas an amyloid patient's going to have shortness of breath and they're going to have maybe neuropathy or they're going to have a lot of swelling and things like that. And so, sometimes it's almost a semantic whether you say amyloid with myeloma or amyloid without myeloma. More times than not, the amyloid is driving the conversation or the treatment.

Now that said, they're both due to those plasma cells, so whether you call them myeloma cells or plasma cells. So the treatments are really going to be very similar, just with a much more cautious look to side effect profile in the patients with amyloid. And so, again, we typically, in the amyloid

space, they may exclude patients with multiple myeloma making it challenging. Like you'd love to use a myeloma drug on like a CAR T or a bispecific T-cell engager or something in an amyloid patient, but they say, "Myeloma but can't have amyloid." So, we're always several years behind the curve in getting the therapies that are good for myeloma, but I think gradually we're going to get everything that myeloma gets, and we just may use it a little bit differently. But certainly, daratumumab is FDA approved for the use in amyloid and that's several years after it was approved in the myeloma space.

Lizette Figueroa-Rivera, MA

Thank you so much. And, Stuart, we also have a podcast that does address this.

The next question is coming from Petrona is asking, "Is it safe to take COVID vaccines with a myeloma diagnosis?"

Angela Dispenzieri, MD

Yeah. I would say yes. There's nothing to suggest that it's not safe. Patients with myeloma, or any cancer for that matter, but myeloma hematologic malignancies are so much more susceptible to have severe disease and so meaning end up in the hospital or, even worse, dying from COVID than other people without those diagnoses. And so, the paradox is also, unfortunately, patients with myeloma or patients on chemotherapy, more correctly, don't respond to the vaccines as well, but that doesn't mean it's dangerous to them. It just means that they don't get the same benefit as perhaps maybe their spouse or family member might get. But I would strongly encourage vaccination, not just COVID but other vaccinations, in patients with multiple myeloma.

Lizette Figueroa-Rivera, MA

Thank you. And our last question today comes from Oiya. Oiya asks, "How do you choose what patients get to do clinical trials?"

Angela Dispenzieri, MD

Yeah. So, in my book, in my mind, we have trials that we think are going to be helpful to patients, so when I see a patient who needs new treatment, there are patients that are doing great, so no clinical trial needed because we don't need to do anything different. We're just happy with how we are. But if there's a time for a change because the disease is progressing or it's a new diagnosis, then we're going to look and see, do we have a trial that matches that patient based on their eligibility, their lifestyle? I live in Rochester, Minnesota, so a lot of our patients aren't local. They're coming from a distance and so sometimes it's hard to put a patient on a clinical trial if they're coming from 2,000 miles away or something; and if they have to come back every week for the trial, well, that's not going to necessarily work for most people. And so, simple things, even like just logistics, doesn't make it

feasible, but if there is a match in terms of the status of the patient, they're eligible and then they're also interested after being educated about it and their options, that's always my first choice.

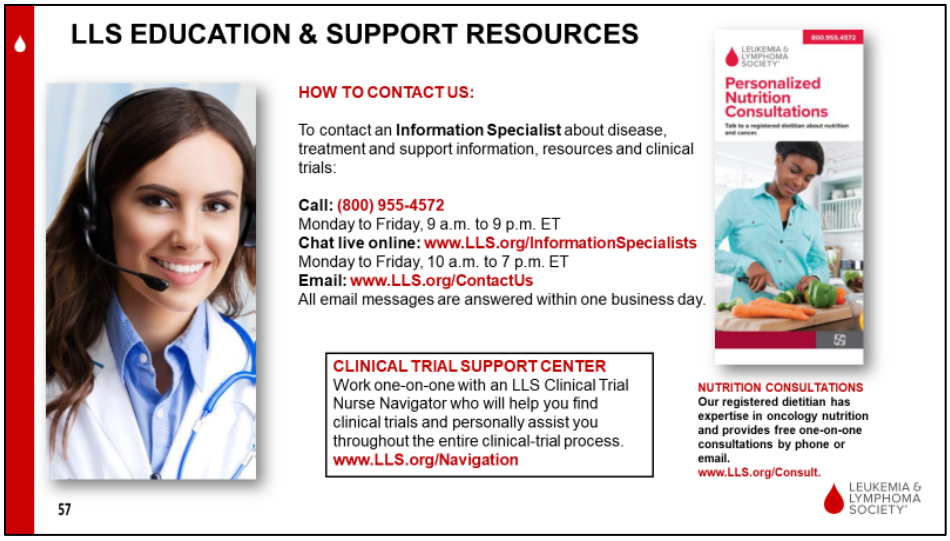
But it's a complex thing. There's life besides myeloma, so people have other commitments, they have other responsibilities, they have things that even if they're, quote, "eligible," it may not fit in with how they can do it. But we try to offer trials to as many patients as possible because we think it's a great opportunity to not only help them, but to provide information for somebody who's diagnosed five, ten years later because we'll be, hopefully, in a very systematic fashion, gathering information about is treatment (a) better than treatment (b) if it's a randomized trial? Or just getting that next drug FDA approved, that next CAR T or that next bispecific or novel therapy.

Lizette Figueroa-Rivera, MA

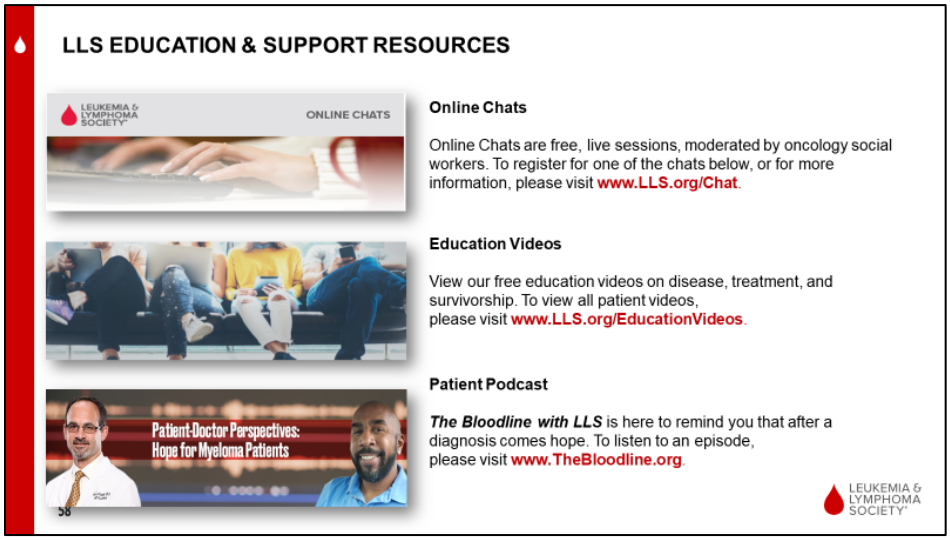
Well thank you so much, Oiya. That was the last question for the day. And thank you so much Dr. Dispenzieri for your continued dedication to patients and for being able to present this program for us today.

CLOSING REMARKS

Lizette Figueroa-Rivera, MA



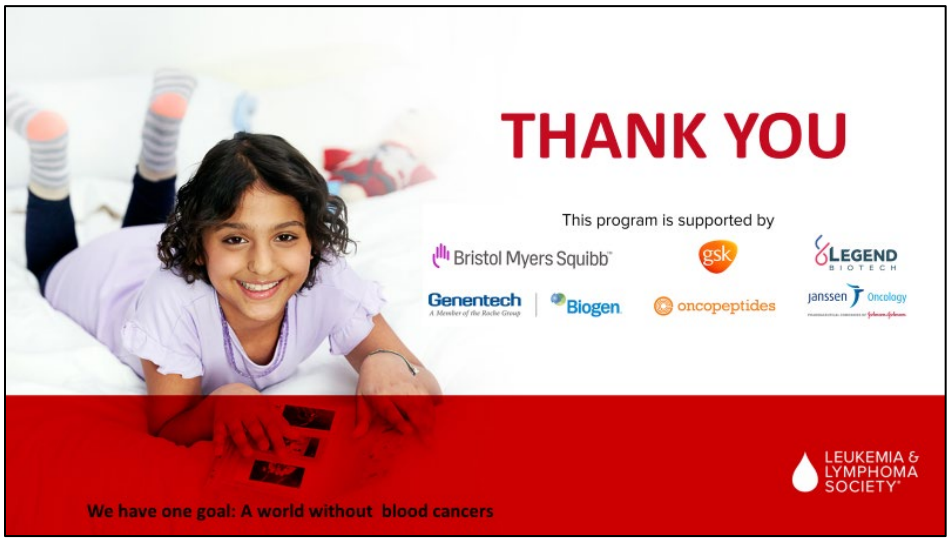
And if we weren't able to get to your question today, you can contact one of our Information Specialists at 1-800-955-4572 and Information Specialists are available to speak with you between 9 AM and 9 PM Eastern Time. You can reach out to us at LLS.org/ContactUs, as well as we have a clinical trial support center (CTSC) that can also speak with you in regard to seeing if a clinical trial is right for you at this time. Clinical trials are available for newly diagnosed patients as well as patients that are relapsed/refractory and so on. So we are here to help you to look into more about clinical trials.



And we do offer a variety of education and support resources, including online chats that are free live forums that are moderated by oncology social workers, and free education videos and podcasts.

LLS offers programs to help individuals with their finances. I know that there were a few questions in regard to the cost of myeloma medications. So please contact us at LLS.org/Finances. And to order free materials LLS.org/Booklets.

Please note that there are not continuing education credits for this program.



Again, we'd like to acknowledge and thank Bristol Myers Squibb, Genentech & Biogen, GlaxoSmithKline, Oncopeptides, as well as Legend Biotech & Janssen Oncology.

Thank you so much, Dr. Dispenzieri, again, for being with us today. The Leukemia & Lymphoma Society wishes all of you well. Thank you for joining us.