WELCOME AND INTRODUCTION

Lizette Figueroa-Rivera, MA

Hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you. Special thanks to Dr. Larry Anderson for sharing his time and expertise with us today. We have over 1,200 people participating in today's program, from across the United States and several countries around the world, including Canada and Burma.

Before we begin, I'd like to introduce Abby Williams, Senior Program Manager, Outreach and Health Promotion at The Leukemia & Lymphoma Society, who will share a few words. Abby, please go ahead.

Abby Williams

Thank you, Lizette. I'd like to add my welcome to the patients, caregivers and healthcare professionals attending the program today.

At The Leukemia & Lymphoma Society, our vision is a world without blood cancer. For nearly 70 years, LLS has invested more than $1 billion in scientific research to find better treatments and cures. We have played a pioneering role in the development of groundbreaking, targeted therapies and immunotherapies that have led to increased survival rates and improved the quality of life for many blood cancer patients.

Though LLS is known for funding research, we are also the leading source of free blood cancer information, education and support. We advocate for survivors and their families helping them navigate their cancer treatments and ensuring that they have access to quality, affordable and coordinated care.

As the Senior Manager of Outreach and Health Promotion, I currently oversee Myeloma Link, the new LLS initiative aiming to address disparities and incidents and treatment that Black Americans experience with multiple myeloma. As Dr. Anderson will touch on today, Black Americans are twice as likely as White Americans to be diagnosed with multiple myeloma. Through Myeloma Link, LLS is partnering with trusted institutions within African-American communities, such as churches and senior centers, to raise awareness about multiple myeloma, signs and symptoms of the disease and resources that LLS offers to myeloma patients and caregivers. The initiative started in January 2017 as a pilot in Atlanta, Georgia and Washington, D.C. and will be expanding to select new cities starting in the fall of 2018.

We're fortunate to have Dr. Anderson as our presenter today. He's one of the nation's leading experts in myeloma. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancer.

On behalf of LLS and all those we serve, I would like to thank him for providing us today with important information for myeloma patients. And now I'll turn the program back to Lizette.

Lizette Figueroa-Rivera, MA

Thank you, Abby. And we would like to acknowledge and thank Amgen, Bristol-Myers Squibb, Celgene and Takeda Oncology for their support of this program.

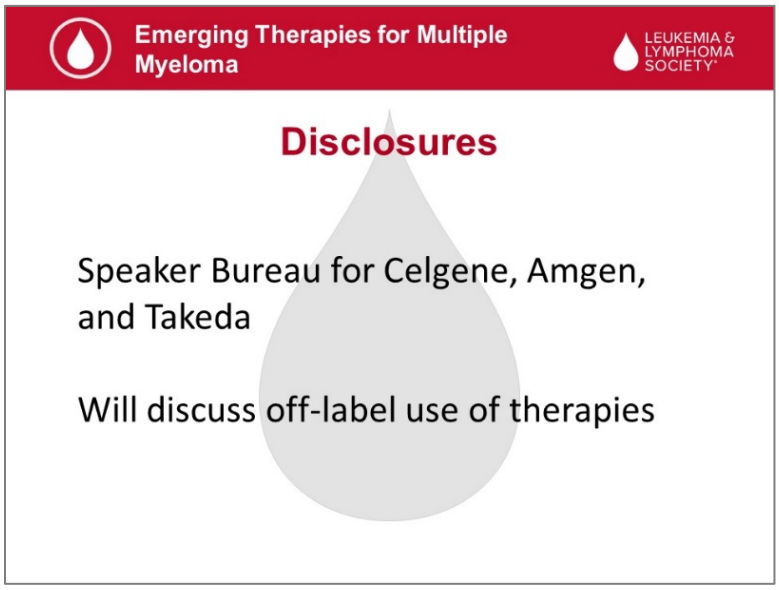
PRESENTATION

Lizette Figueroa-Rivera, MA

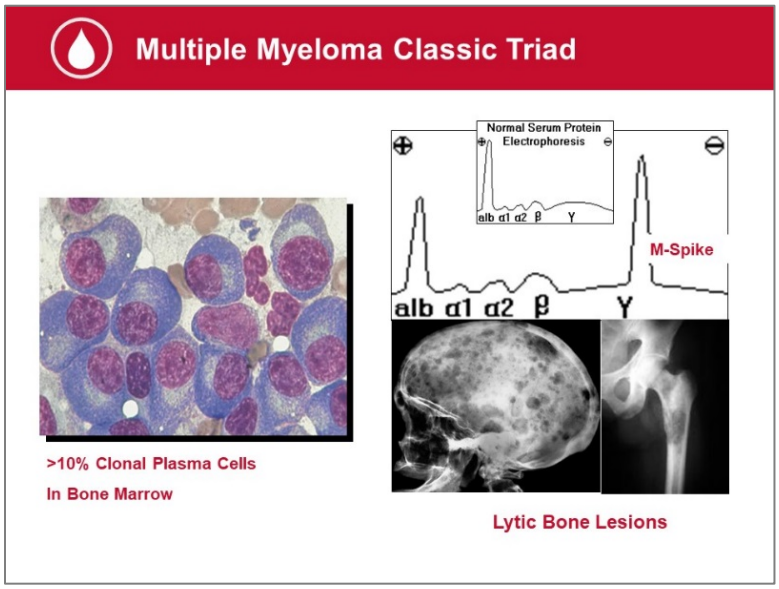
I'm now pleased to introduce Dr. Larry Anderson, Associate Professor of Internal Medicine, Director of Myeloma, Waldenströms and Amyloidosis Program and Attending Hematologic Malignancies, Blood and Marrow Transplantation Program at UT Southwestern Medical Center, Simmons Comprehensive Cancer Center in Dallas, Texas.

On behalf of The Leukemia & Lymphoma Society, thank you so much for volunteering your time and expertise with us today, doctor. And now I'm privileged to turn the program over to you.

Larry D. Anderson, Jr, MD, PhD

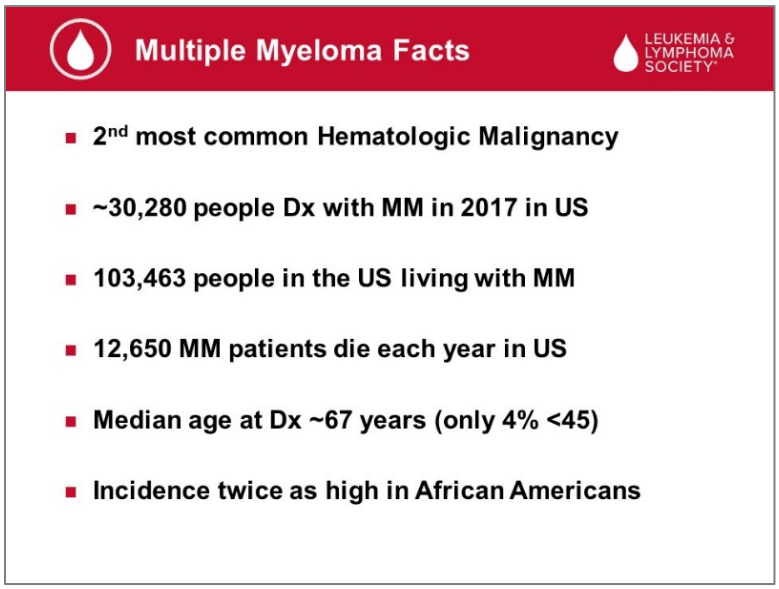


Thank you so much. It's an honor and a privilege to be here and to talk to patients about myeloma, a subject near and dear to my heart. As a myeloma specialist, I deal with these things every day, but it's good to be able to get this out to the community and let people know what kind of exciting therapies that we have that we're able to offer our patients now as standard of care and what some of the really cool and exciting therapies and trials are looking like as well.



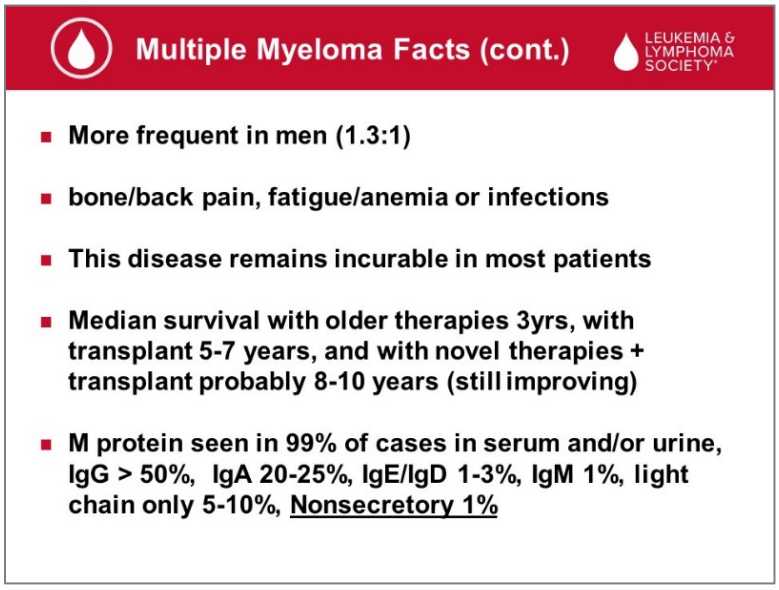
So just as a little bit of a background, what is multiple myeloma? It is a bone marrow cancer of plasma cells, which are part of our immune system; normally secrete these proteins called immunoglobulins or antibodies. These plasma cells become mutated, their DNA becomes mutated over the lifetime of the patient, usually in several different places, and causes those cells to grow uncontrollably and take over more than 10% of the bone marrow space by definition and they produce all the same size protein. And so, when we separate out the proteins, we can see them show up as a spike on the electrophoresis because there's a whole bunch of the same exact size protein.

These plasma cells also cause destruction of bone, and these bone lesions called lytic lesions are pretty characteristic in X-rays. And so, these plasma cells and a monoclonal spike and bone lesions are the hallmark of many patients with myeloma.



It is the second most common blood cancer, second only to non-Hodgkin's lymphoma. Over 30,000 patients are diagnosed each year in the US, and this is one of the few cancers where the incidence is gradually increasing and not decreasing. Many patients, well over 100,000 patients are living with myeloma in the US. But, unfortunately, we still can't cure myeloma with the current treatments and so many patients still die each year, although I will show you later that the survival is dramatically improving over the past decade.

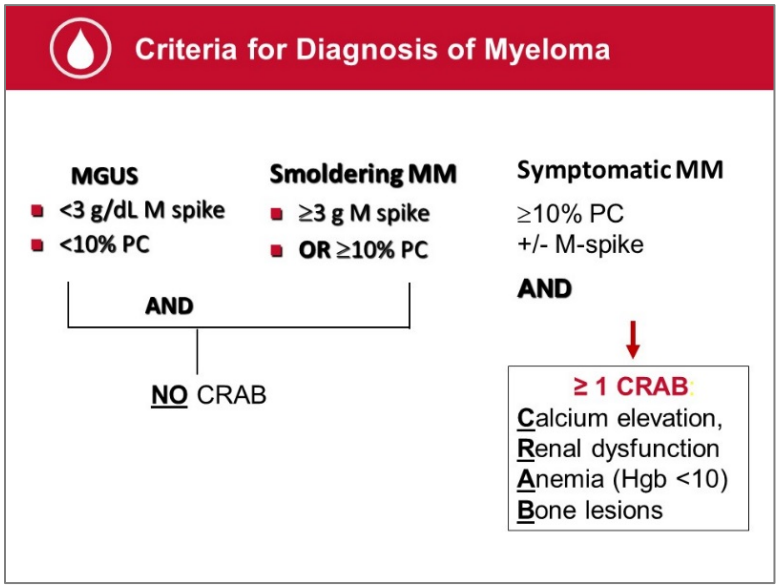
These patients are generally, on average, around 67, but we certainly have patients in their 20s and 50s and 80s, all ranges, but only 4% of the patients are under 45. As was mentioned, this disease is twice as common in African Americans.



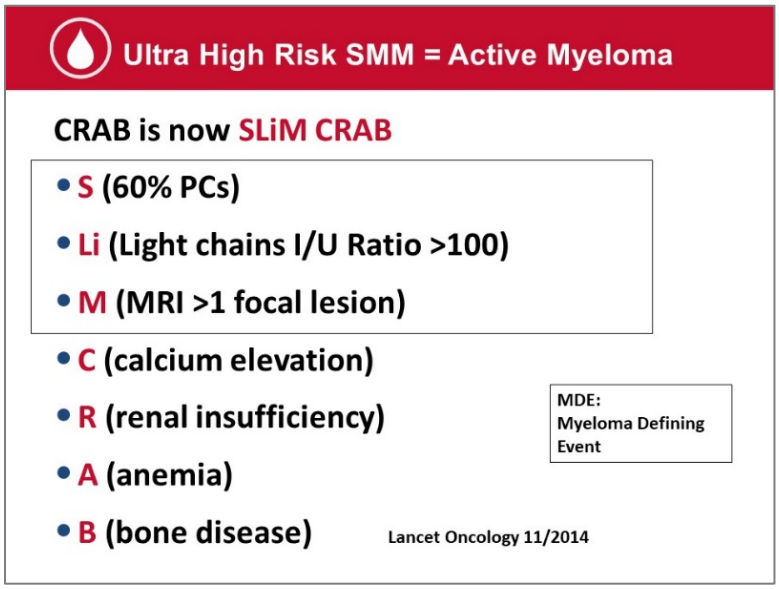
It is also slightly more common in men, but we certainly see plenty of women with myeloma. The most common presenting symptoms of myeloma would be bone or back pain because of these lytic lesions and compression fractures of the spine. Also, another most common presenting feature would be fatigue from anemia. The plasma cells crowd out the normal production of blood cells and so the patients have really low hemoglobin in many cases. And, also, they can have low immune system which leads to frequent infections. One of the things that other patients could get would be kidney failure or high calcium.

This disease, as I mentioned, remains incurable. Many years ago, when I was in fellowship training, we would say that survival was about three years. And then with stem cell transplant, when it became common, the survival improved by a few years. But then now that we have all the current treatment options, many are estimating that half of the patients are living longer than eight to ten years and that number keeps getting better and better. Most of these patients will have a protein made by their myeloma called IgG or immunoglobulin G, but a quarter of them may have an IgA. It's very rare that someone would have an IgM or IgD immunoglobulin subtype, but about up to 10% of patients may have light chain only myeloma, which is just a little piece of the immunoglobulin called the light chain.

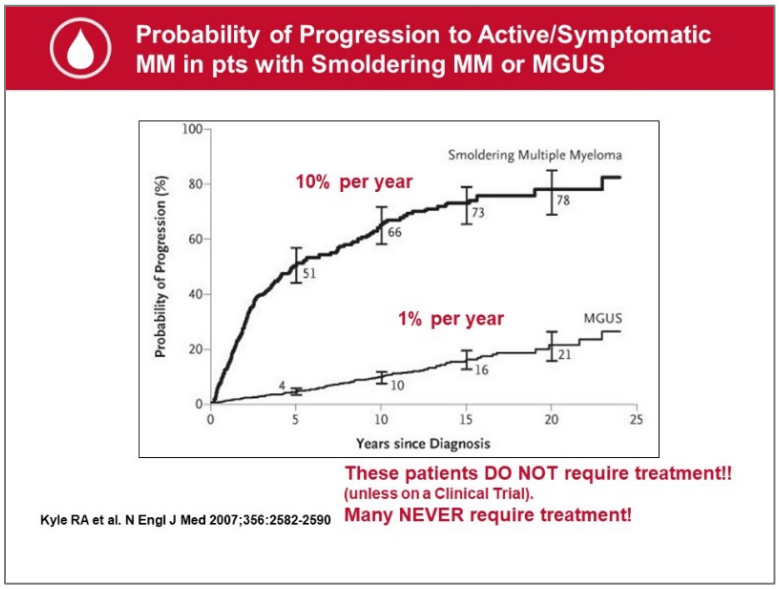
And less than 1% of patients would be what we call nonsecretory where we can't find any monoclonal protein or light chains in the blood or urine.



So, let's say we have a patient with a monoclonal protein on the electrophoresis that was done for some reason on their blood work, what does that mean? Does everyone have myeloma? Certainly not. If we check the blood of everyone over 50, about 3% of people on the street would have a monoclonal protein in their blood, and that would be most commonly referred to as monoclonal gammopathy of undetermined significance or MGUS. By definition, their monoclonal spike is less than 3 grams per deciliter, and if you do a bone marrow biopsy, they have less than 10% plasma cells. But let's say they do have a spike that's over 3 or they have more than 10% plasma cells, by definition, that has to be at least smoldering myeloma, which is in between MGUS and symptomatic myeloma. Patients that have smoldering myeloma meet the criteria for diagnosis, but they don't have something called CRAB symptoms. They don't have high calcium or kidney failure or anemia or bone lesions. And those patients are at higher risk for developing symptoms from myeloma, but some of them never do. And so, we typically observe those patients for smoldering myeloma, and we really watch for signs of CRAB criteria.



In addition to CRAB criteria, more recently in the past few years, we also now have something that I refer to as SLiM CRAB criteria. So, we have three more criteria that are now referred to as myeloma-defining events that would signify the need for treatment of the myeloma. Before we would just watch these patients, but now we know if the patient has 60% plasma cells – S in SLiM is for 60% – we are needing to treat those patients because they're almost guaranteed to develop symptoms within two years. And the Li in SLiM is for light chain ratio over 100. Those patients are at higher risk for developing kidney failure and symptomatic myeloma, so we treat those patients usually. Also, MRI is now pulled into the screening of these patients with smoldering myeloma. We would look for focal bone marrow lesions in more than one place, and we would consider treating those patients as well. So now that we have better treatments that are less toxic, we could start treating a little bit earlier patients. There are also clinical trials in smoldering myeloma for treatment, but that's not a standard at the moment.



This is just a graph showing how likely it is a patient is to develop symptomatic myeloma if they have either MGUS on the bottom curve there or smoldering myeloma. So, with MGUS, there's about a 1% per year risk of going on and developing symptoms, whereas with smoldering myeloma, it's about 10% risk per year. But even then, after 20 years of follow-up, a quarter of these patients may never need treatment.

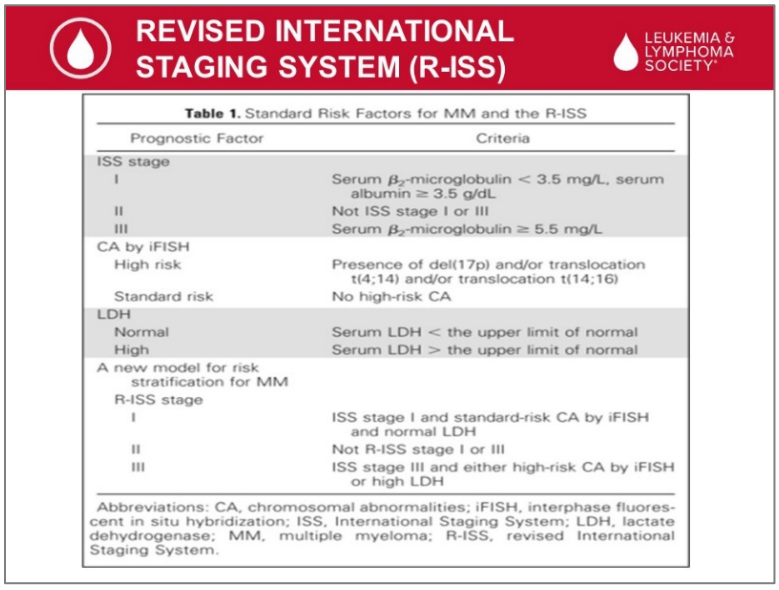
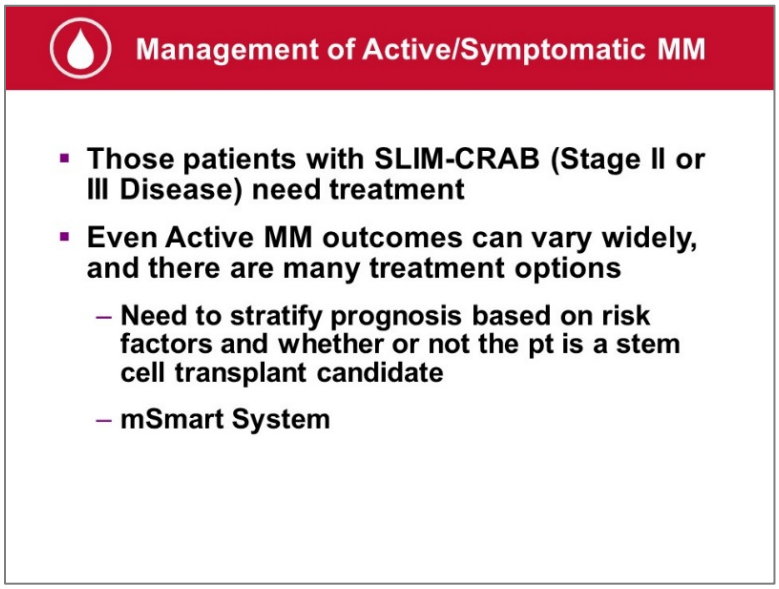


Table 1. Standard Risk Factors for MM and the R-ISS

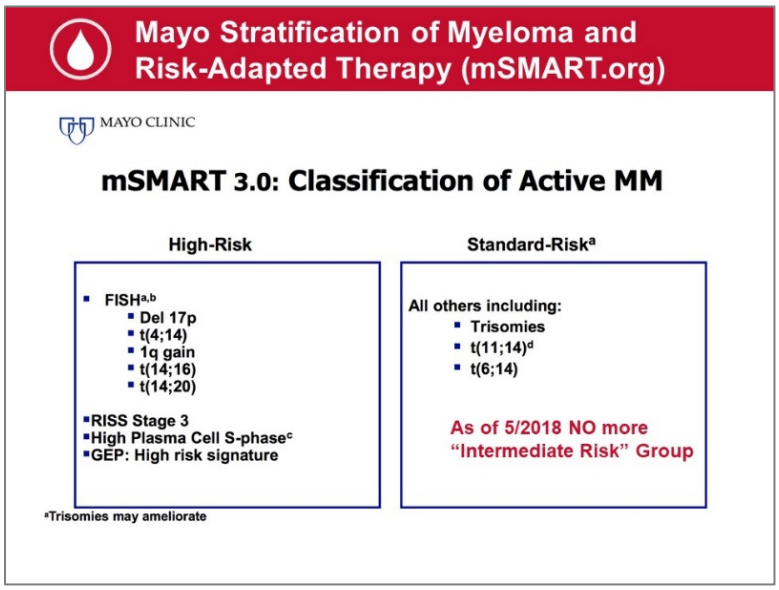
Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.

The staging system currently used for multiple myeloma is called the Revised International Staging System (R-ISS). You don't have to memorize these things, but just wanted to point out that we use a couple labs called the beta-2-microglobulin (B2M) and the albumin that's detected on the bloodwork. And now we've incorporated the chromosome changes from the bone marrow plasma cells into the staging system to determine if a patient is high risk.

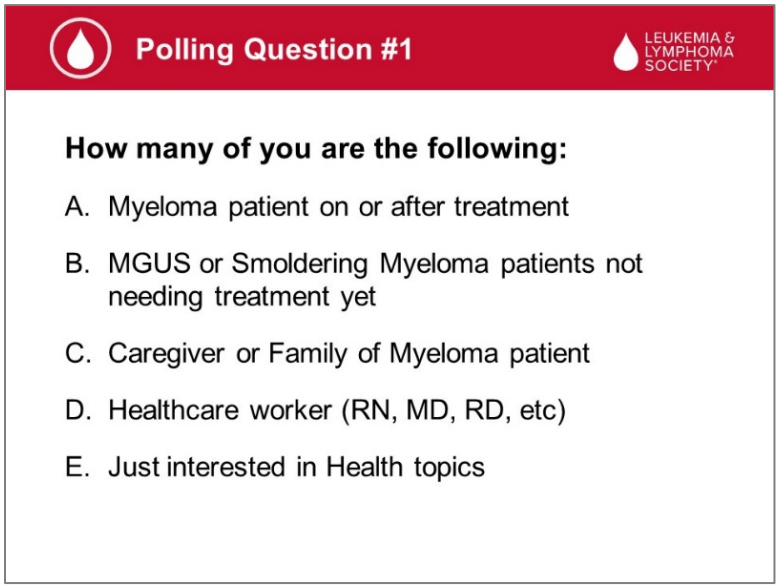


So, what do we do if we have a patient that needs treatment? One of the tools that we have to determine how aggressive we should be or how aggressive the treatment should be is a system that the Mayo Clinic has devised called the mSMART system. If you go to the mSMART.org on the Internet, you can find this.



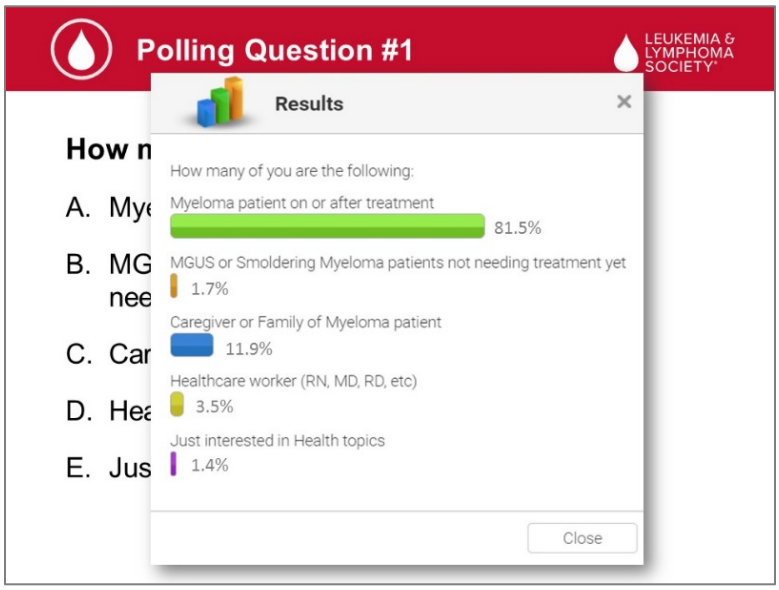
They, actually, just recently changed this whole system last month. We did have high, intermediate and standard risk myeloma, but now they've omitted the intermediate risk – and we are left with just two categories, high risk and standard risk. The high-risk features would be something that we see in the myeloma cells, and those would include deletion of chromosome of 17p or translocation of 4;14 or 14;16, for example. And if patients have those markers, we would tend to be a little more aggressive

or at least make sure we give patients the benefit of the doubt and give everything that we would normally have to offer.



Before we go further into the treatment options for myeloma, just wanted to take a polling question for the audience, at least the ones that can see the Web and type in. Wanted to find out, number one, (A) if you're a myeloma patient on or after finishing treatment, or (B) if you have a premyeloma state such as MGUS or smoldering myeloma but not needing treatment yet, or (C) if you're a caregiver or family of the myeloma patient, and (D) if you're a healthcare worker, like a nurse or a doctor or a dietician, etc., or (E) just because you're interested in health topics and wanted to find out more about myeloma.

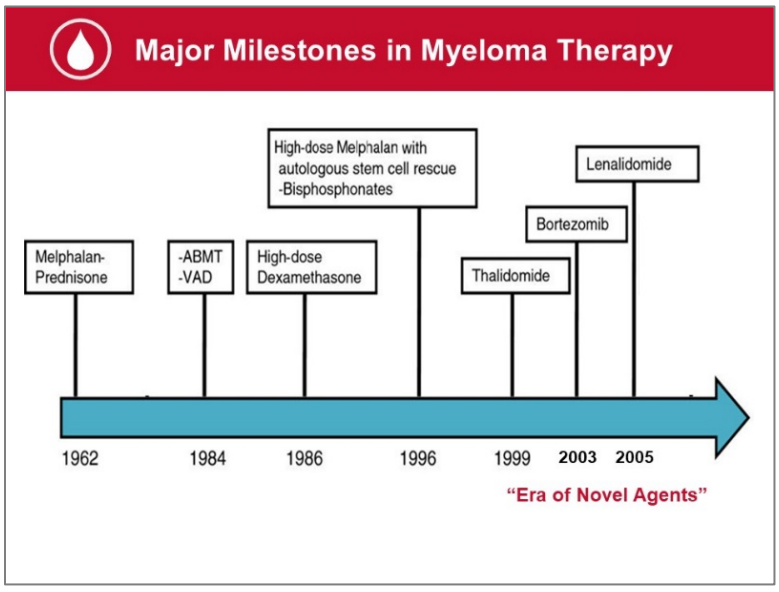
Lizette Figueroa-Rivera, MA



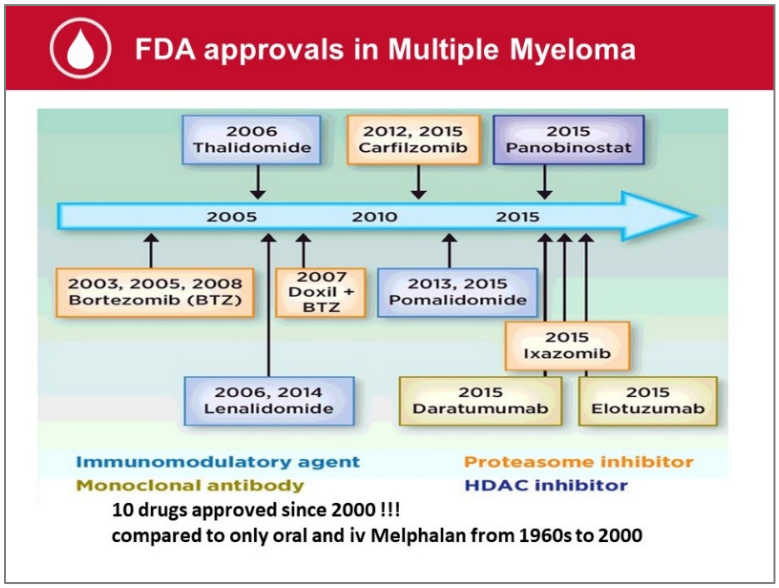
We have 81.5% myeloma patients on or after treatment, 1.7% MGUS or smoldering, 11.9% caregivers or family members of myeloma patients, 3.5% healthcare workers, and 1.4% just interested in health topics.

Larry D. Anderson, Jr, MD, PhD

Excellent. Okay, thank you. So, a lot of patients on here, that's really good, and then a lot of caregivers as well which is important. Okay, so let's move forward.

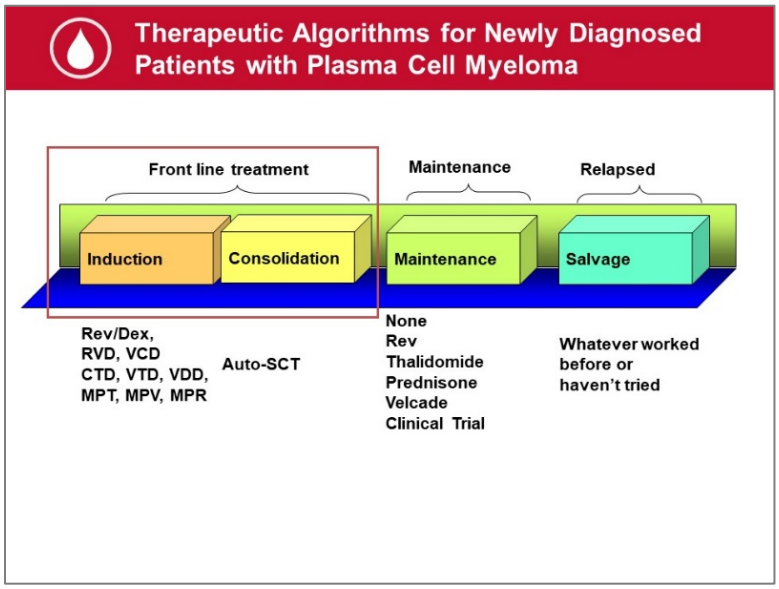


So, the exciting thing in myeloma is that we have a lot of treatment options now, which we did not have for many decades. So, between 1960s and 2000, really, all we had was oral melphalan and then later on high dose IV melphalan with stem cell transplant and a few other things that weren't really shown to have improvement in survival compared to melphalan. But since 2000, since the turn of the Century, we've had many new drugs approved. The first one that was tested that's in the class of something we call novel therapies was thalidomide. And then that led to a slew of other options with many targeted and nontoxic therapies. First bortezomib, then lenalidomide.



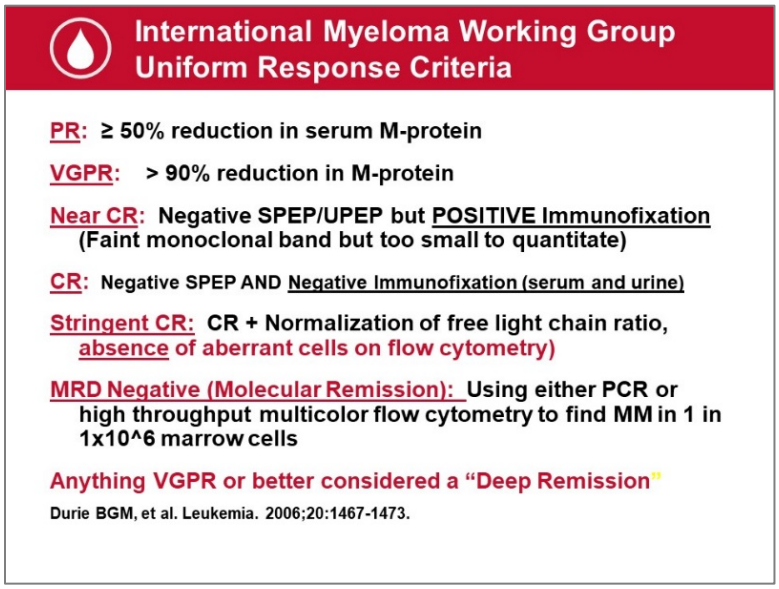
We've had ten drugs approved for myeloma since 2000. So, we have a lot of different options these days, and we've made a lot of progress in myeloma thanks in part to organizations like The Leukemia & Lymphoma Society that helps get these studies and drugs approved.

So, we've got several classes of medications now, but we've got proteasome inhibitors, we've got immunomodulatory drugs, we've got both oral agents, IV agents. We've got monoclonal antibodies.



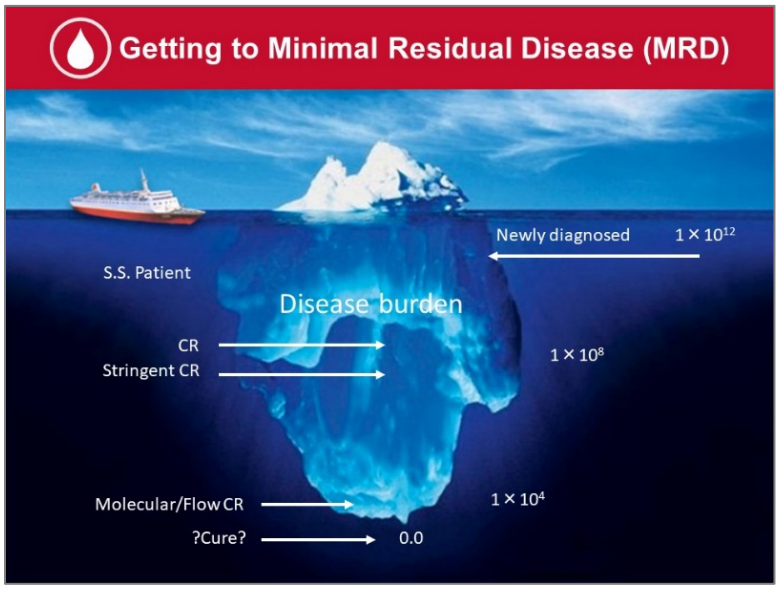
Once a patient starts on these treatments, we typically refer to the treatment in four different phases.

So, when a newly diagnosed patient is started on therapy, we call that induction therapy. We're trying to induce a remission. Many different options there. Once they're in a remission, after four cycles or so, then we try to consolidate that remission with either a stem cell transplant or sometimes further therapy. And then, once they're done with their more intensive therapy, most patients these days we're trying to maintain their remission with maintenance therapy, the most common of which would be lenalidomide. And then, if someone relapses, then we go into relapse or salvage therapy.

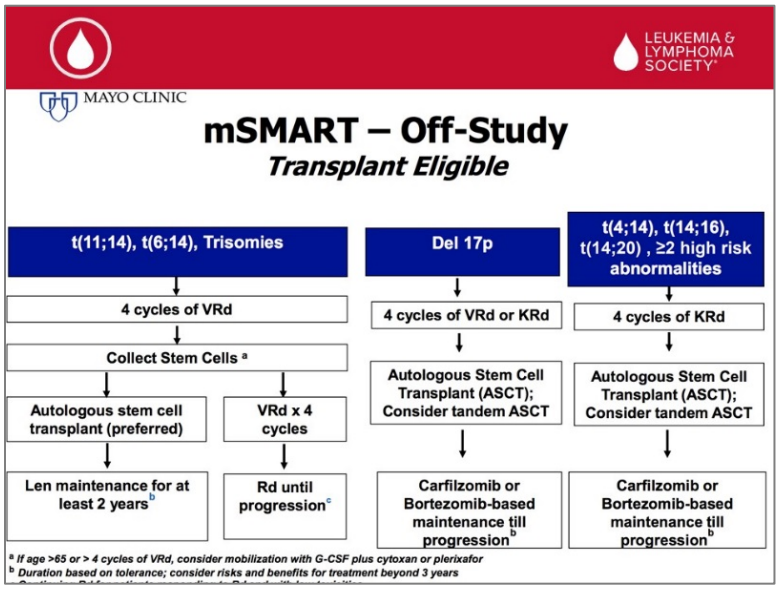


When we talk about remission in myeloma, it can be multitiered in the definition, so all remissions are not the same. So, the minimum we would like to see to call someone in a partial response or partial

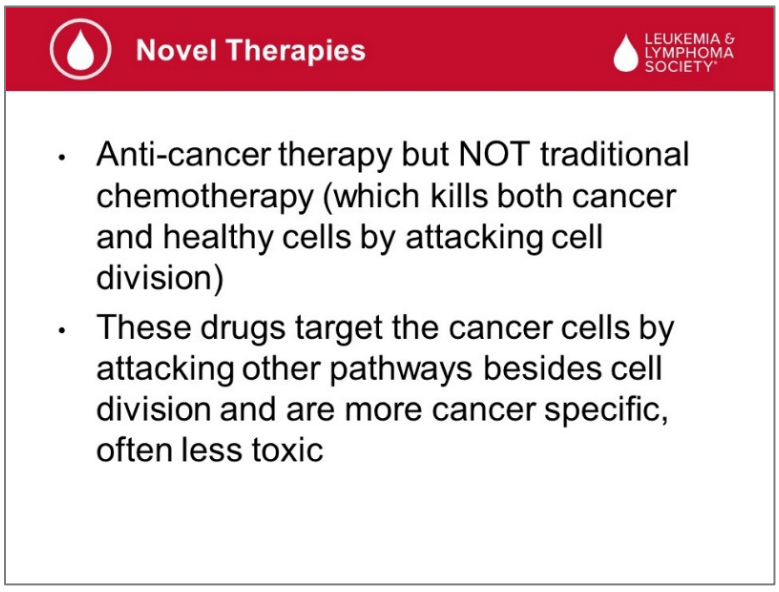
remission would be a 50% drop of their myeloma protein or M-protein. If we have a 90% drop, we call that a very good partial remission, or VGPR, and anything 90% or above would be considered a deep remission (DR) in most experts' opinion. We also have some further categories of a near complete remission (nCR) where the monoclonal protein is too small to quantify, and they just have a faint amount of it. And a complete remission (CR) is when we can't detect the monoclonal protein by immunofixation, a very sensitive test to look for these things, in the blood or the 24-hour urine. We also have a category called stringent complete remission (sCR) if they have not only complete remission by blood and urine but, also, normal light chain ratio and normal bone marrow flow cytometry. And a lot of the studies these days are looking for something even deeper called a molecular remission or negativity for minimal residual disease or MRD negative you'll hear a lot in the studies. And that may signify very deep remission. And that could be either done by high sensitivity flow cytometry testing of the bone marrow, or molecular sequencing studies that have to be sent out to be done.



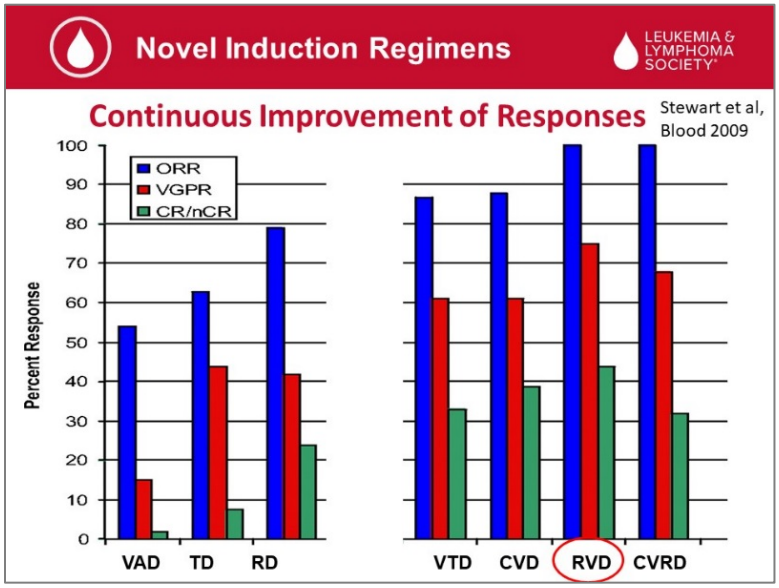
So, when we look at myeloma markers in the blood, we're sort of looking at the tip of the iceberg. And even if we can't find the myeloma protein in the blood, we know there's still some cells hanging out in the bone marrow somewhere, and that's why we're starting to do these more sensitive tests and look for molecular remissions or MRD negative status.



So, once we're starting someone on treatment, we tend to go back to the mSMART system and look and see what are the current national recommendations? And these are guidelines; they're not absolutes. There are certainly many different reasons why one patient would have one treatment, a different one have another treatment. Every patient I look at as individuals that we have to really take all of their particular characteristics, not only their disease but their living situation, their comorbidities or other diseases, whether or not they have neuropathy, whether they have other cancers. All of these things come into play when we decide on treatment. But most of the patients these days are receiving triple therapy with drugs like bortezomib, lenalidomide and dexamethasone or VRD followed by stem cell transplant and then maintenance therapy.

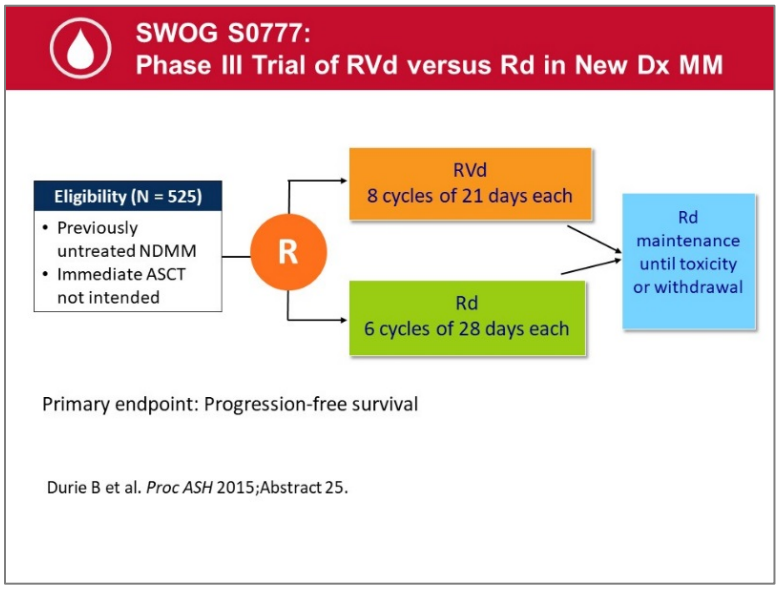


So, when we talk about novel therapies, what are we talking about? So, these are generally anticancer therapies that are not traditional chemo, so they don't just kill every dividing cell like traditional chemotherapy does. They usually don't make you lose your hair, they don't make you sick at your stomach, and so they're more targeted.

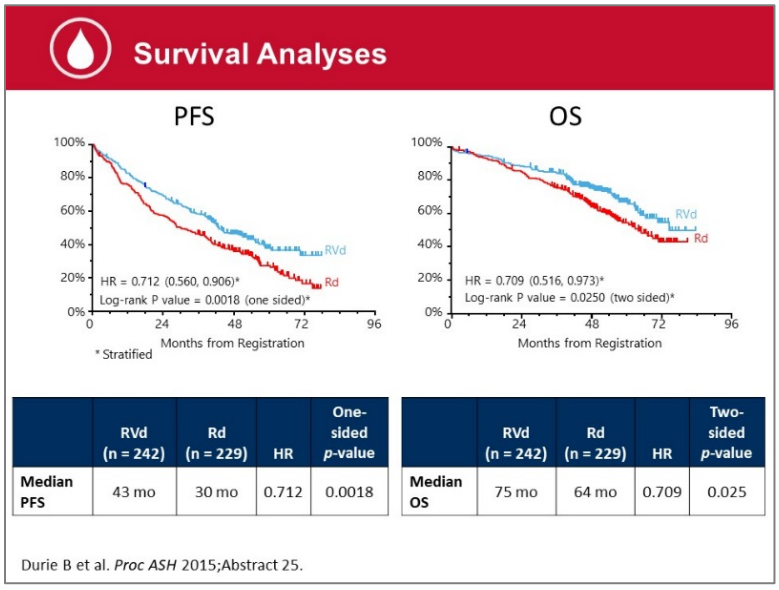


When we start combining these drugs, we see really remarkable responses in myeloma. Historically, with melphalan and with this other treatment we used to use called VAD with vincristine-Adriamycin (doxorubicin) and dexamethasone, we would see maybe half the patients would have a response, but very few deep remissions. Now that we're using combinations like the RVD, as I have circled here, with Revlimid® (lenalidomide) and Velcade® (bortezomib) and dexamethasone, we're seeing 97% response rates and over half the patients are getting into a deep remission and 40-50% are in complete remission. So, we're really seeing remarkable improvements in levels of remission and duration of remission.

People have tried adding a fourth drug, for example, adding Cytoxan (cyclophosphamide) to the Revlimid and Velcade and dexamethasone without really any further improvement in the responses but just added toxicity. So, right now most patients are not receiving a fourth drug in their upfront therapy. However, current trials are looking at whether or not we can add the less toxic monoclonal antibodies upfront. So that might be something that's done in the near future.



One of the reasons that we used this particular triplet combination, RVD or Revlimid-Velcade and dexamethasone, is because of the randomized clinical trial that looked at 525 patients that had newly diagnosed myeloma and they were randomized to either triple therapy with Revlimid-Velcade and dexamethasone versus doublet therapy with Revlimid and dexamethasone. And then they stayed on Revlimid maintenance.

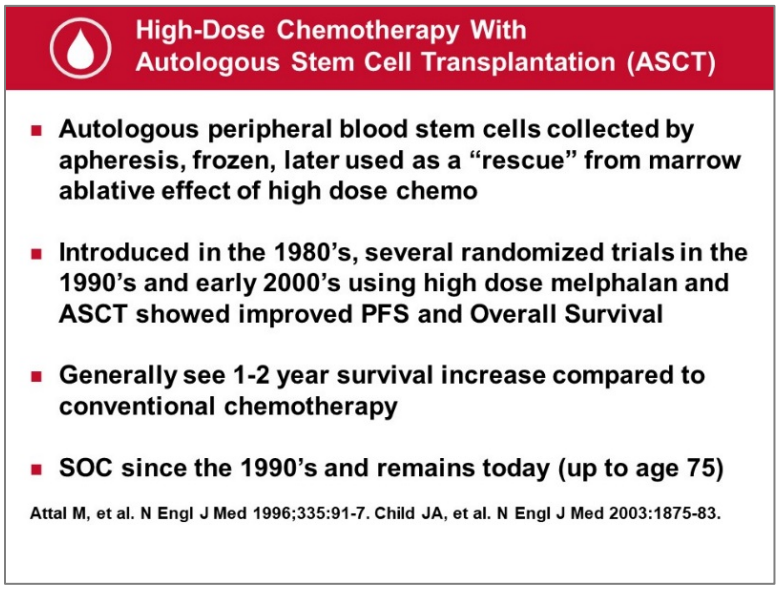


	RVd (n = 242)	Rd (n = 229)	HR	One-sided *p*-value
Median PFS	43 mo	30 mo	0.712	0.0018

	RVd (n = 242)	Rd (n = 229)	HR	Two-sided *p*-value
Median OS	75 mo	64 mo	0.709	0.025

Not only did we see that the remissions lasted, on average, much longer, instead of 30 months for the doublet therapy, it was improved to 43 months on average of remission from the triple therapy but, also, the overall survival was improved by about ten months, from 64 months to 75 months, with this therapy So this largely led to this therapy becoming a standard of care.

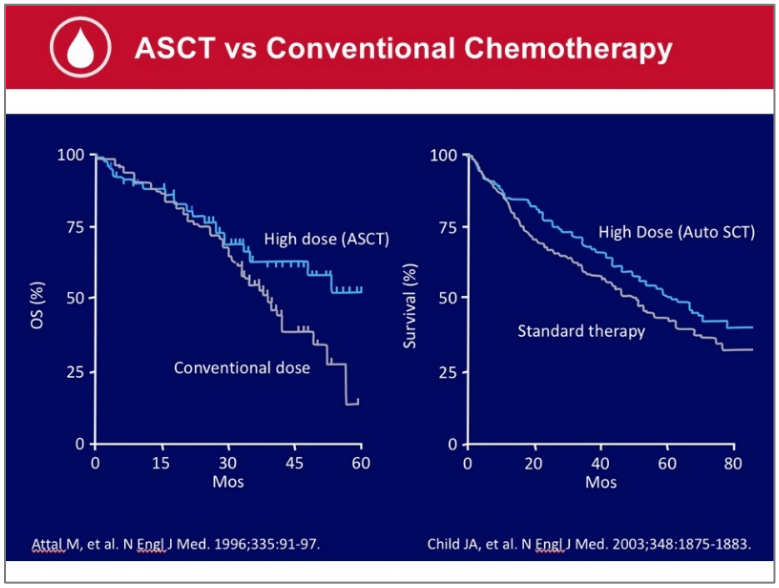
And I just wanted to point out one of the things that this webcast is focusing on is side effect management and long-term complications and quality of life. And just wanted to point out that when patients are on these therapies with combinations of therapy, we want to make sure the patients are letting their health professional team, like the nurse giving the treatments and the doctor, letting them know if they're having side effects so that we can adjust accordingly. For example, one of the main toxicities of this therapy that includes Velcade or bortezomib would be peripheral neuropathy. And, in order to have that longer remissions and longer survival, we have to be able to stay on the treatment. And, if you're having neuropathy, we want to make sure that we're dose adjusting, you know, reducing the dose and make sure we're giving it as a subcutaneous shot instead of IV to help prevent neuropathy. And in cases where it's more severe, we can hold off on the treatment and then lower the dose and sometimes go to once weekly. So that's all key to being able to stay on these treatments. And, likewise, with the long-term Revlimid, if you're having side effects, we need to make sure we adjust that dose so that you're not throwing up your arms and saying, "I'm done."



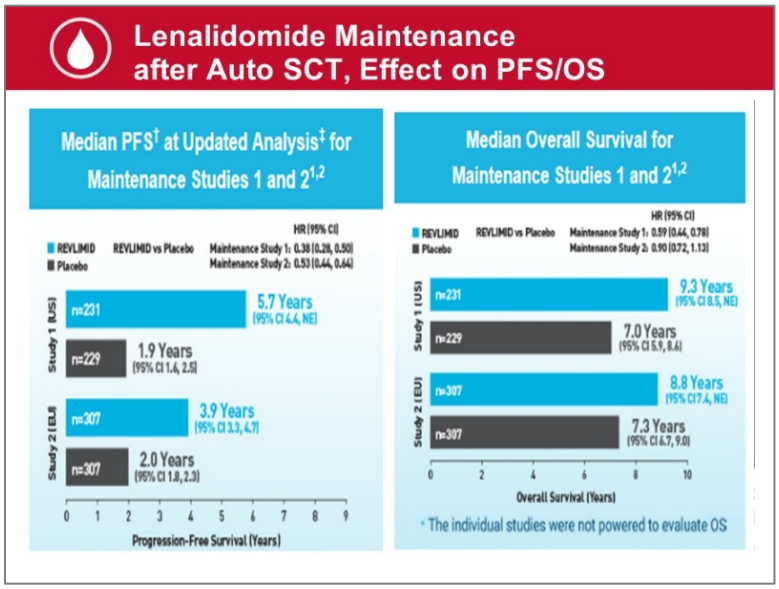
So, once we get patients in a decent remission with their first three or four months of treatment, then currently the standard of care would be to move on to a stem cell transplant for patients up to the age of 75. However, this is certainly not an easy treatment, so this is much less targeted than the novel therapies we talked about. This still involves a high dose of the traditional chemotherapy called melphalan. The whole point of the autologous stem cell transplant is to give the patient a high dose of this chemo to wipe out as much of the residual myeloma as possible. And before we can infuse the chemo, we have to collect the patient's stem cells from their blood. And we do that with some growth factor shots called Neupogen® (filgrastim) and others. And those stem cells collected out of the blood can then be frozen and then reinfused a couple days after the chemo to rescue the bone marrow, to replace the bone marrow. And so, the stem cells are not embryonic stem cells. They're hematopoietic stem cells that are able to give rise to all the different types of blood cells.

So, there's a few different interchangeable terms for this. Many people refer to it as a bone marrow transplant because these stems cells originally came from the bone marrow. When we infuse them

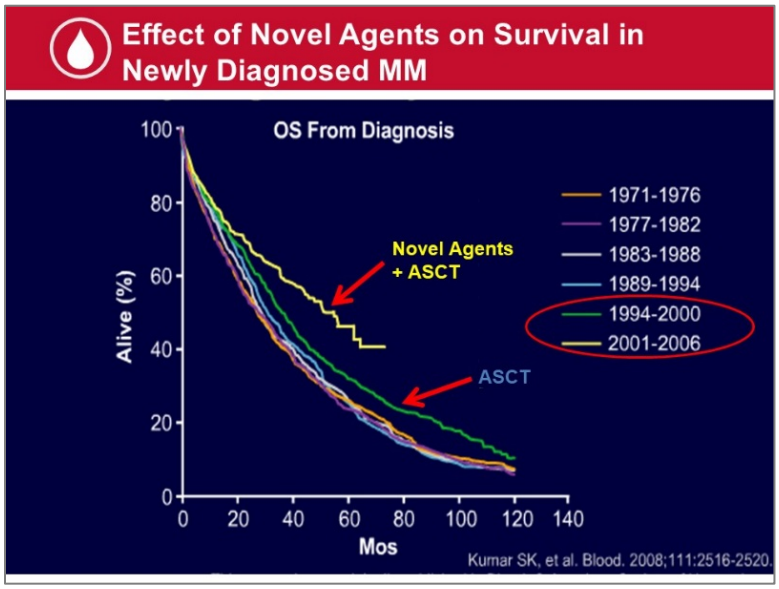
back into the patient, they go back into the bone marrow and replace it. We also call it autologous peripheral blood stem cell transplant, it's the same thing. And it's autologous because auto means self, so we're using the patient's own stem cells. In leukemia and lymphoma, there are many transplants done using other donors and those are called allogeneic transplants, and those have a lot higher risk with them like graft-versus-host disease (GVHD). And we don't typically do those for myeloma except in special cases or in clinical trials. There's no studies proving benefit in myeloma right now. But there is proven survival benefit with stem cell transplant, at least compared to the older treatments, and generally improved survival by a couple years. And it's become a standard of care since the '90s.



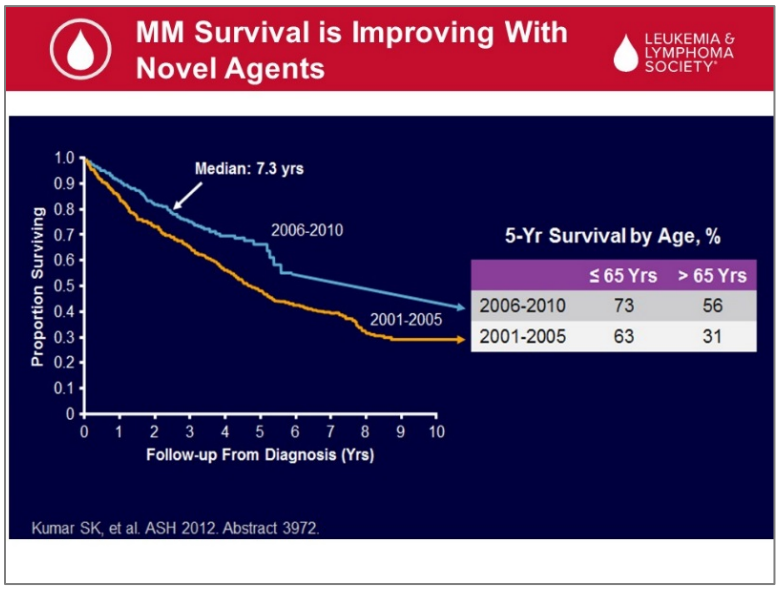
These are a couple studies showing that the overall survival was improved in two different studies looking at high-dose chemo in stem cell transplant versus what was then standard chemotherapy.



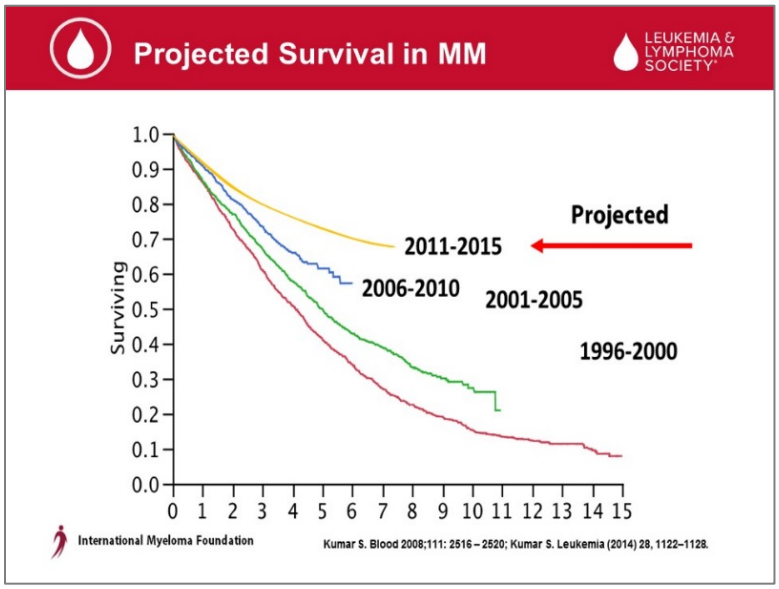
So, let's say the patient has gone through induction therapy, transplant; now what do we do? Many patients these days are going on maintenance therapy with lenalidomide or Revlimid because of this data, and it has become FDA approved. So, on the left, you'll see the progression-free survival. That's how long patients stayed without progression. And there's two different studies here. The top set of blue and gray bars are from America and the bottom set are from Europe. And both studies looked at the same thing but just showed two different studies proving the same thing. The progression took much longer in patients that were on maintenance lenalidomide. On average, without the maintenance therapy or with a placebo, they were only in remission for about 2 years after transplant compared to closer to 6 years with maintenance therapy in the American study, so tripled the progression-free survival or time to relapse. And in the European study, it went from 2 years without maintenance to almost 4 years with maintenance. Also, not only were the patients in remission significantly longer, but they also lived longer. So, the overall survival is how long they lived, and it went from 7 years in America without maintenance to 9.3 years with maintenance. And then in Europe it went from 7.3 to 8.8. So, both studies showed significantly improved overall survival.



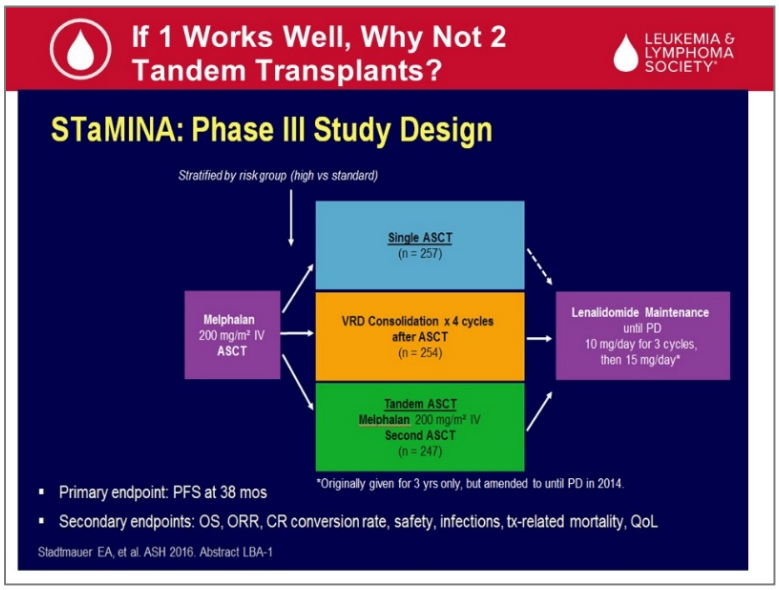
Because of these survival advantages we're seeing with upfront treatment, with transplant and with maintenance therapy, we are now starting to see these advances in survival that we had been talking about. So, if you look at all the survival of myeloma patients in the '70s and '80s, really nothing came along that was improving survival until the advent of high-dose chemo and autologous stem cell transplant; we see the green line there starting to separate. And then, since the turn of the century with novel therapy plus transplant, we're starting to see even better separation.



And, more recently, if you look at the early 2000s versus the mid-2000s, we continue to see improvement in survival. And especially in the patients over 65, you'll notice that the survival has doubled from 2000 through until 2010 from 31% to 56% of patients alive at five years.

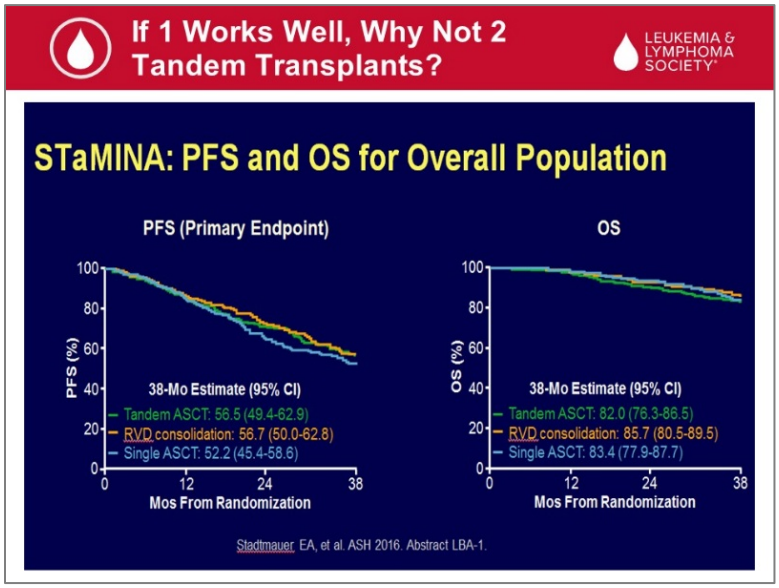


Many experts are estimating that the survival with myeloma continues to improve, and half the patients are still alive at eight to ten years out. So, you see the more recent figures from the later 2000s so that these curves continue to improve with all the treatment advances we have.

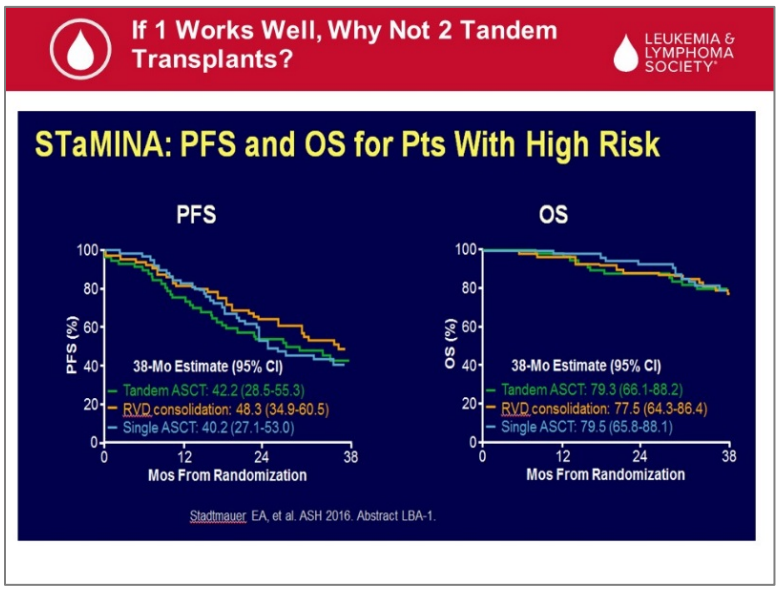


So, let's say we know that doing transplant seems to improve things. What if we did a second transplant, and what if we went back and did, if we didn't do a second transplant, what if we gave more Velcade instead of going straight to maintenance therapy? That was the question in the StaMINA study that was reported a few years ago looking at three groups of patients. They randomized them to either just a single autologous transplant followed by maintenance versus a transplant and then consolidation with four cycles of Velcade before moving to lenalidomide

maintenance versus a second transplant, called a tandem autologous transplant, before moving to maintenance.

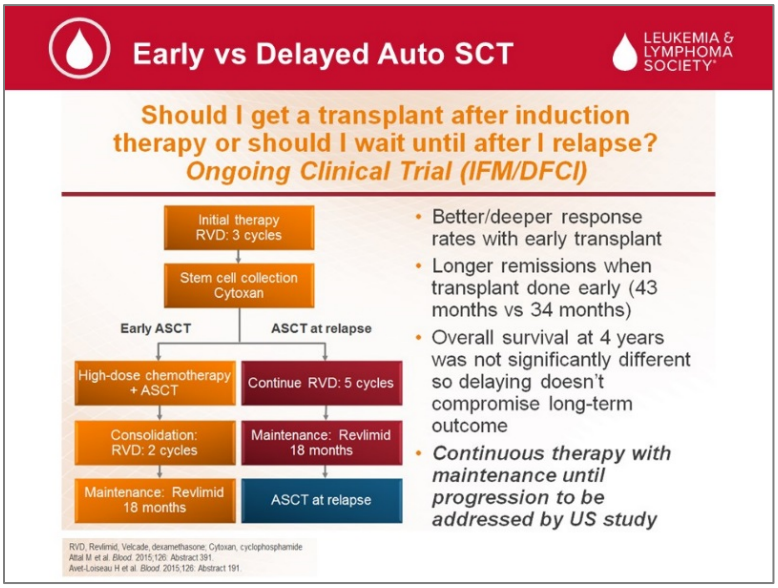


Interestingly, even though this tandem transplant is often done in Arkansas, and many groups had standardly done this, we now know that with this randomized study, there was really zero difference between one and two transplants. So, so far there was no change in the length of remission or survival with the second transplant in myeloma.



So, then we said, “What if we just break down the groups and look at just the high-risk patients with the bad chromosome changes? Can we see a difference there?” No, we still did not see a difference. So, right now the standard of care would be one transplant rather than two.

Now there is some data from a European registry study that does indicate that high-risk patients in certain situations may benefit from a second transplant, so it’s still something to be considered for the really high-risk patients. But just in general, it would be one transplant.

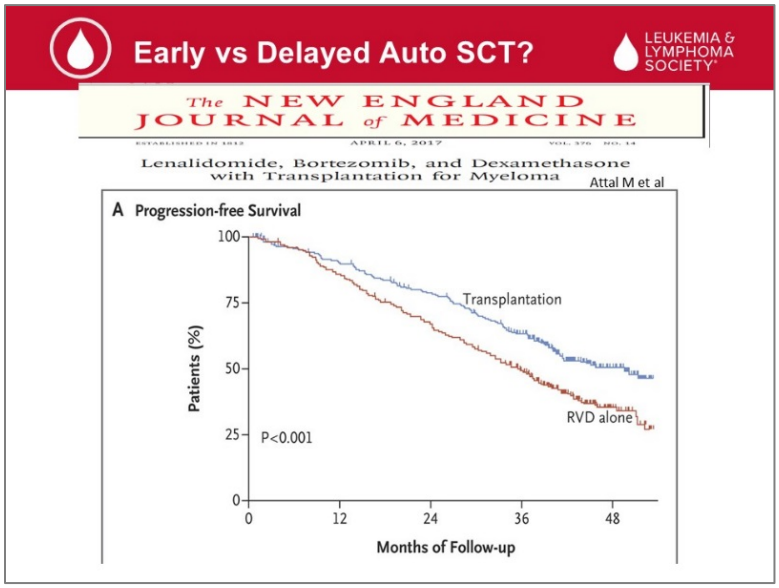


So, let’s say now that we know that all these treatments are working really well, now that we have all of these great treatment options, now that we’re not using traditional chemotherapy to compare the transplant with, can we get by with delaying the transplant until relapse? And so, the Dana-Farber along with the French group developed a study that we refer to as the Dana-Farber study. And then in parallel, part of it was done in France with the International Francophone Myélome group, IFM. And the French data has been reported. The American study is ongoing, and we haven’t reported any data yet. We just recently finished getting patients enrolled in that study. But the French data has been reported. And in the study, what we did was we took patients with newly diagnosed myeloma, gave them three cycles of triple therapy with Revlimid-Velcade and dexamethasone followed by stem cell mobilization. Half the patients went straight to stem cell transplant as per standard of care and then maintenance therapy, but the other half just collected and stored and went back on Velcade and Revlimid for five more cycles and then maintenance therapy and saved the transplant for relapse.

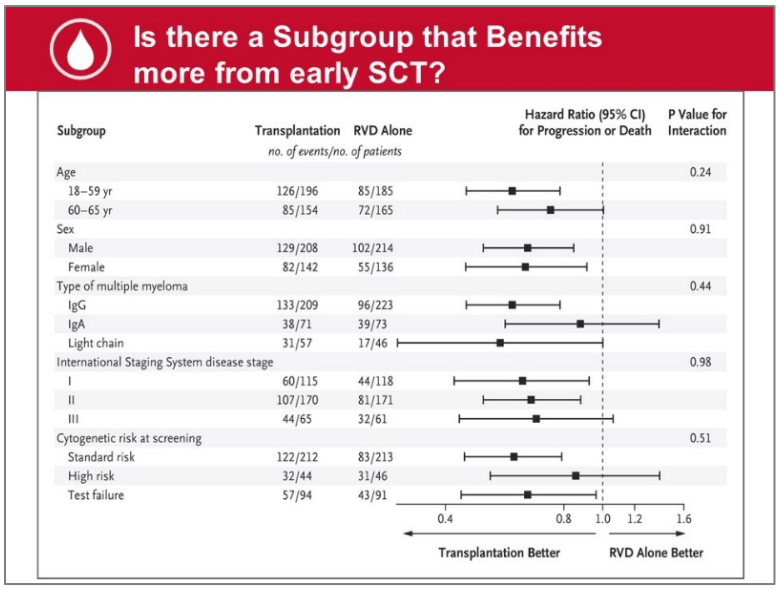
What the French study showed was that this transplant in first remission did induce deeper remissions, longer remissions – on average 43 months compared to 34 months. However, we can’t say that the survival was better at this point. So far, the survival looks the same because we have so many other options for when the patient relapses.

Another notable thing in the French study, they stopped their maintenance therapy a little after a year, whereas in the American part of the study were continuing on maintenance indefinitely until

progression. So, we're not stopping it. And we're hoping that staying on maintenance may help change the progression-free survival.

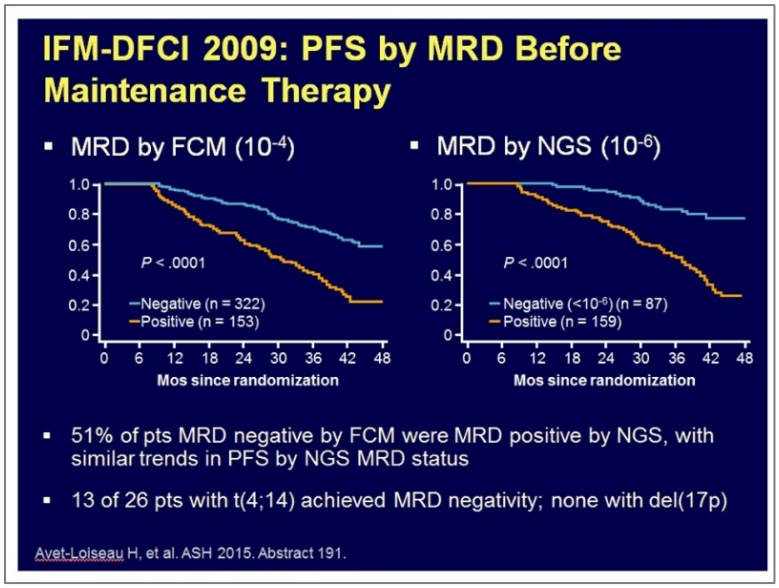


So, this was the French data showing that the patients that went through the early transplant had longer remissions, longer progression-free survival. But we're hoping that those curves might, actually, come together if we stay on maintenance after the first year. So, the jury is still out on that.

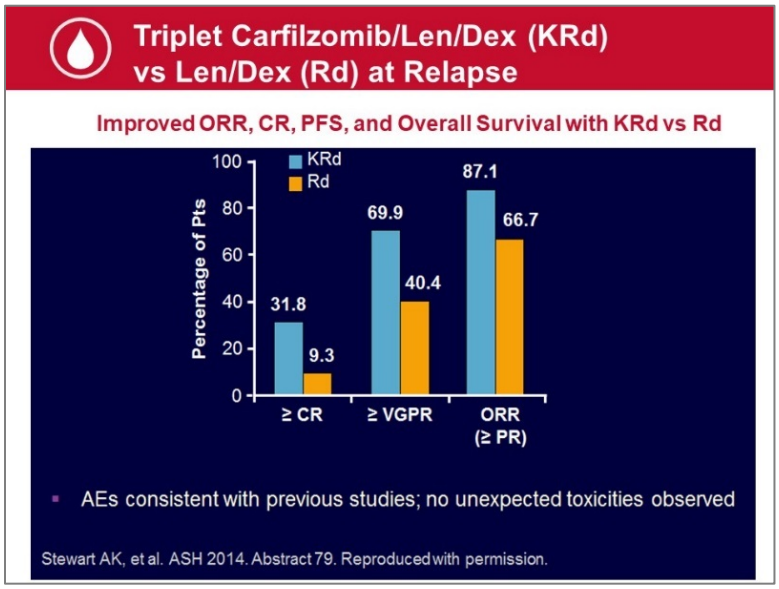


The next question is, well, did the early transplant benefit just a certain subgroup of patients? But, no, it appears to have benefit for all the different groups regardless of age, sex, subtype or cytogenetic risks. Even the high-risk patients benefited from the early transplant versus the delayed. But, certainly, because the survival is the same, we can at least offer this to patients that are in a, offer the

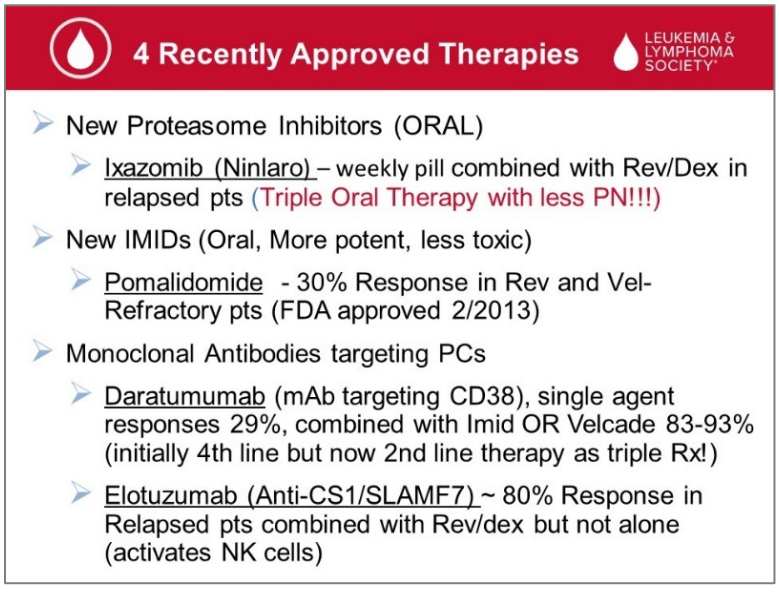
collect and store option to patients that are in a good remission and that really don't want to do the transplant. We can at least feel more confident that it is an option at this point.



So, what about the patients that are in this so-called molecular remission or MRD negative? This study helped further prove that these patients that are in a molecular remission have superior remissions and outcomes compared to the ones that don't achieve molecular remissions. Now what we don't yet know is in those patients in molecular remission, can we stop their maintenance therapy? Or, on the other hand, many are advocating looking at trials where, instead of stopping for negative testing, we're actually just saying, "Those patients are doing well, benefiting from treatment. The ones that are testing positive for molecular minimal residual disease may need further intensification of their treatment." So many studies are ongoing looking at what to do and should we intervene and do something different? But, right now we don't really know how to use this data. We just know that the patients in molecular remission do better.



Okay, let's say a patient has relapsed after their initial treatment down the road. Hopefully, many years down the road. But when they have their myeloma protein starting to rise, then what do we do? One of the options is triple therapy with carfilzomib-lenalidomide and dex (dexamethasone). The trade names are Kyprolis™ (carfilzomib), Rev (Revlimid, bortezomib) and dex, so that's why we see the acronym KRd used a lot. So, this study, it's called the ASPIRE study, did a randomized comparison of triple KRd therapy versus double lenalidomide and dexamethasone therapy at relapse and found that not only did significantly more patients respond to the triple therapy, but we really, essentially, tripled the complete remission rates and significantly improved the deep remissions with relatively well tolerated therapy.

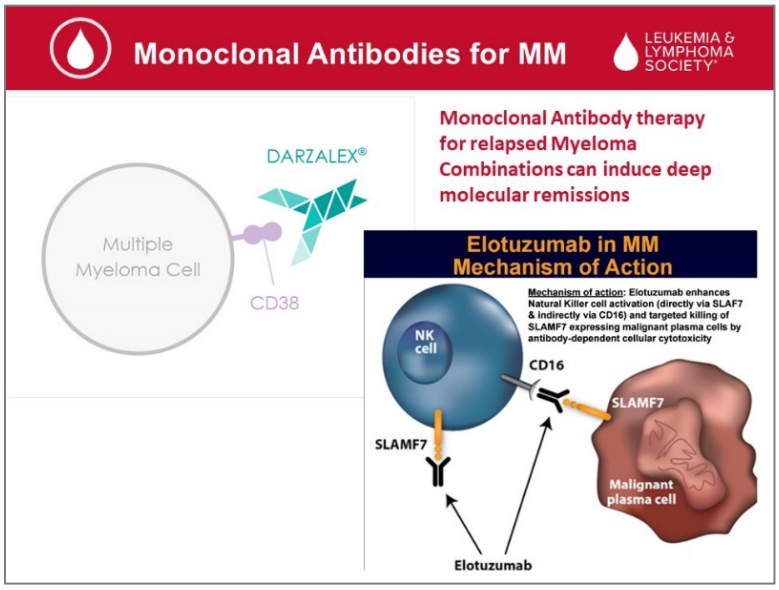


So Kyprolis is one option for relapse. We also have several other options, including an oral proteasome inhibitor now. So Kyprolis is an IV proteasome inhibitor and bortezomib was a subcutaneous. Now we have an oral proteasome inhibitor called ixazomib or Ninlaro®. And when combined with Revlimid and dexamethasone, we have triple oral therapy that works really well and has less risk of peripheral neuropathy compared to the subcutaneous Velcade.

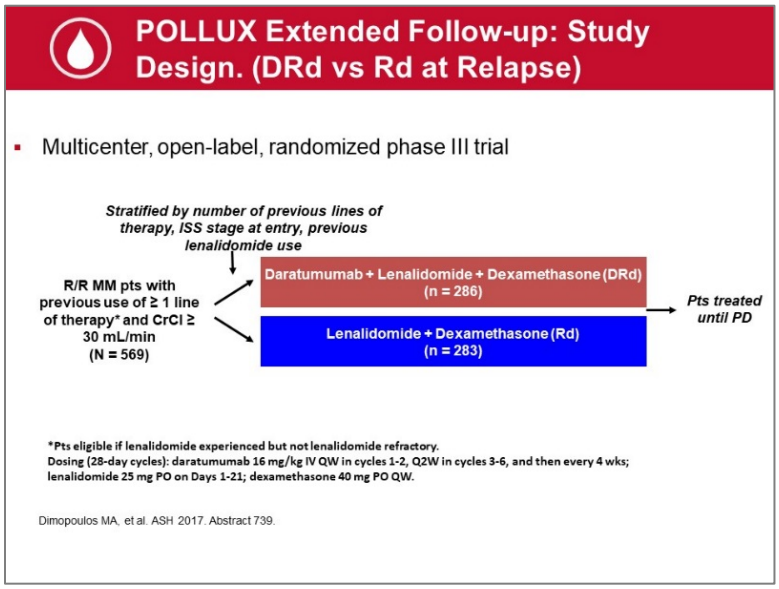
We also have another oral therapy for relapsed patients called pomalidomide that works in about a third of the patients who failed Revlimid even though it's in the same class as Revlimid and many of the same side effect risks.

Even more exciting is now we have two different monoclonal antibodies that are FDA approved. We have daratumumab that targets CD38 on the surface of the myeloma cells. By itself, works in about a third of the patients. But when combined with either Revlimid or Velcade, works in close to 90% of the patients that relapse. It was initially FDA approved as fourth-line therapy as a single agent, but now it's FDA approved as a second-line therapy when we combine it with either an IMiD (immunomodulatory drug) or a proteasome inhibitor. And a lot of patients are getting this second line now.

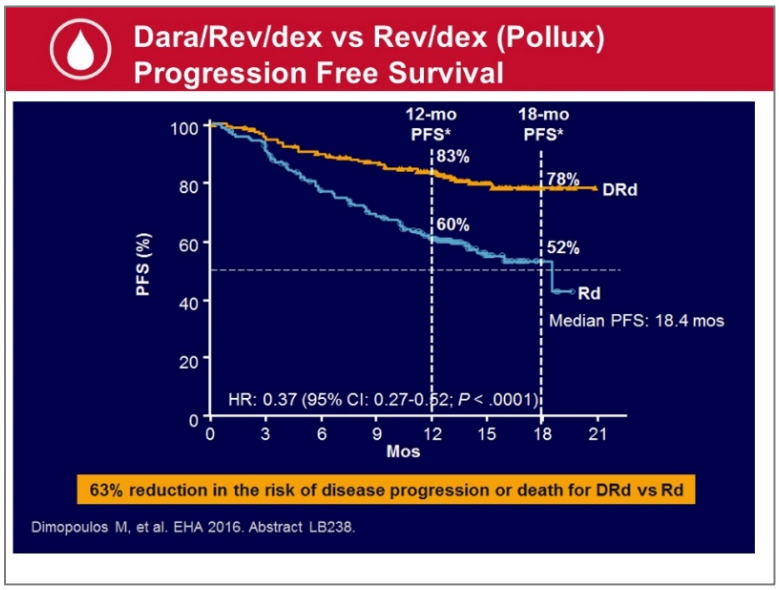
Another monoclonal antibody that we can use second line is elotuzumab, which targets a different molecule on the surface of the myeloma called SLAM F7 (Signaling Lymphocyte Activation Molecule family 7) or CS1. It induced about 80% responses when combined with Revlimid. It also is thought to activate natural killer cells and doesn't really have activity in myeloma when it's given by itself. So, it has to be given with an IMiD for activity, probably because both the IMiD and the elotuzumab activate natural killer cells.



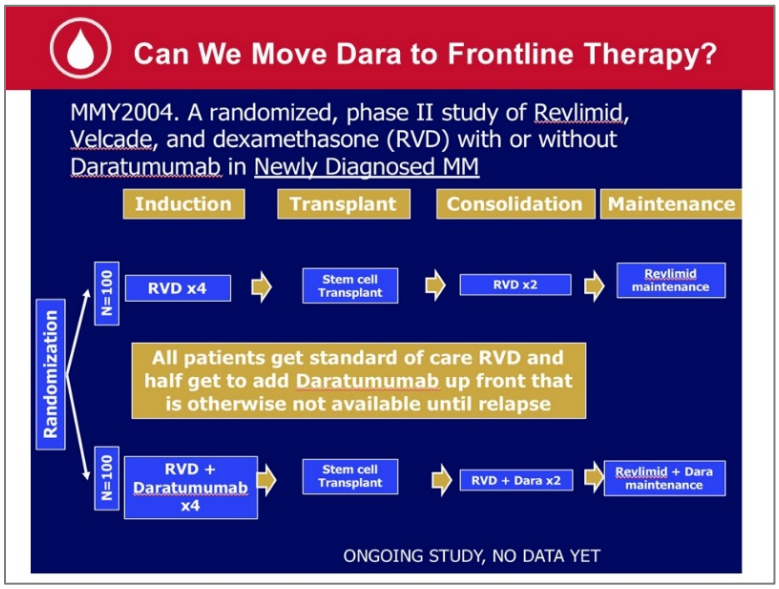
So, this is those two antibodies just showing that they're targeting different molecules on the surface of the myeloma.



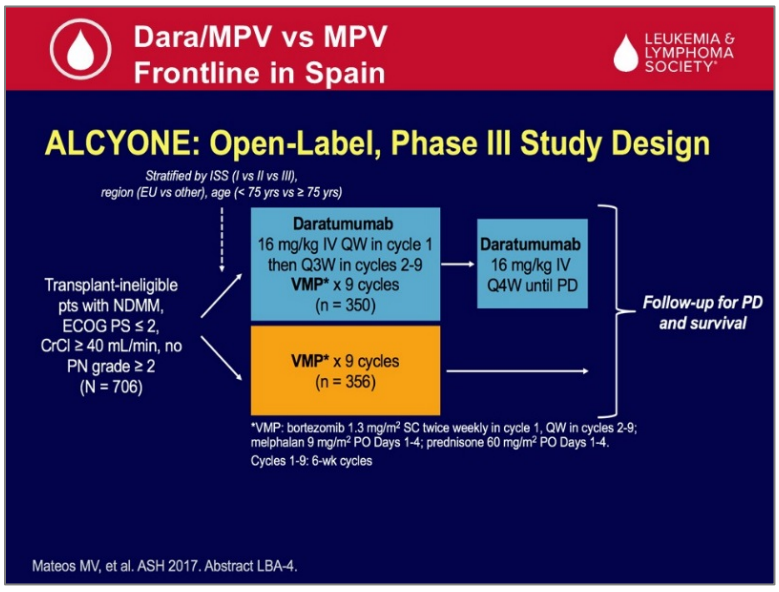
So now that we have this monoclonal antibody daratumumab, just wanted to show you the data that led to approval in second-line therapy. So, a randomized study looked at triple therapy with daratumumab, this anti-CD38 antibody, combined with oral lenalidomide and dexamethasone. Compared it with just the lenalidomide and dexamethasone in relapsed patients.



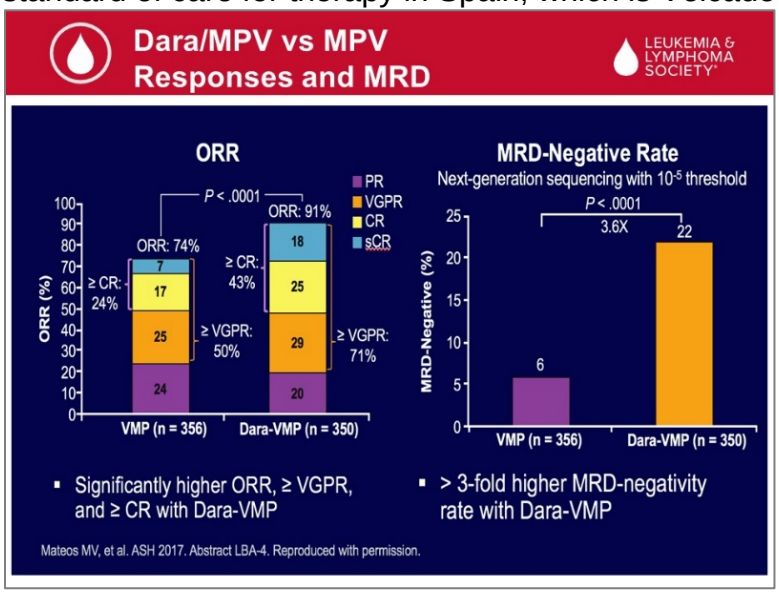
And we see that the remissions lasted significantly longer in the daratumumab triple therapy compared to the Revlimid and dexamethasone only.



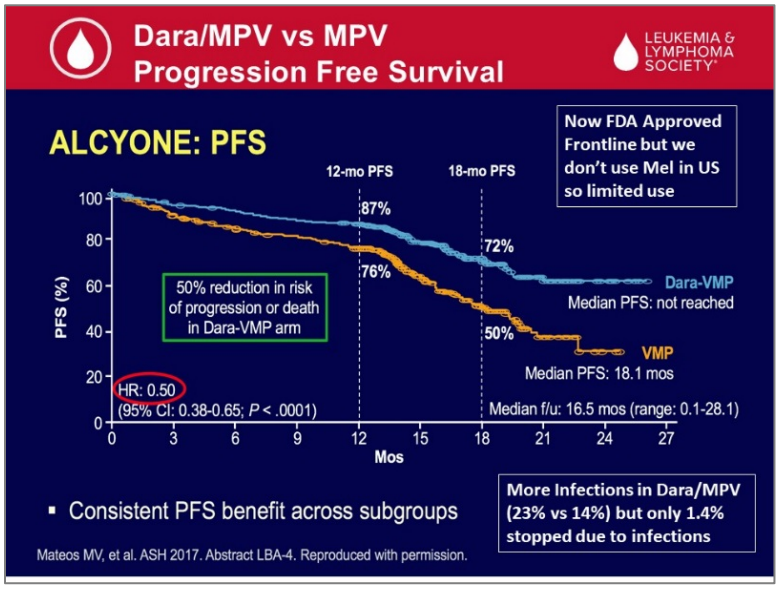
Now that we know that daratumumab is very effective in relapse disease, and not to mention it is very low risk of side effects, what if we were to move it to front-line therapy? So now there are different studies looking at combining it with induction therapy. So, we at UT Southwestern have participated in this study, as have several groups around the country, called the GRIFFIN study looking at combining daratumumab with the triple Revlimid-Velcade-dexamethasone induction therapy and randomized to with or without the daratumumab along with RVD. And we don't have any readout on this study yet, it's ongoing, but all the patients have been accrued to the study so, hopefully, within the next year, we'll get some results from that study. And this could be a practice-changing finding eventually.



In the meanwhile, another study in Europe has looked at combining daratumumab with the current standard of care for therapy in Spain, which is Velcade-melphalan and prednisone, or VMP.

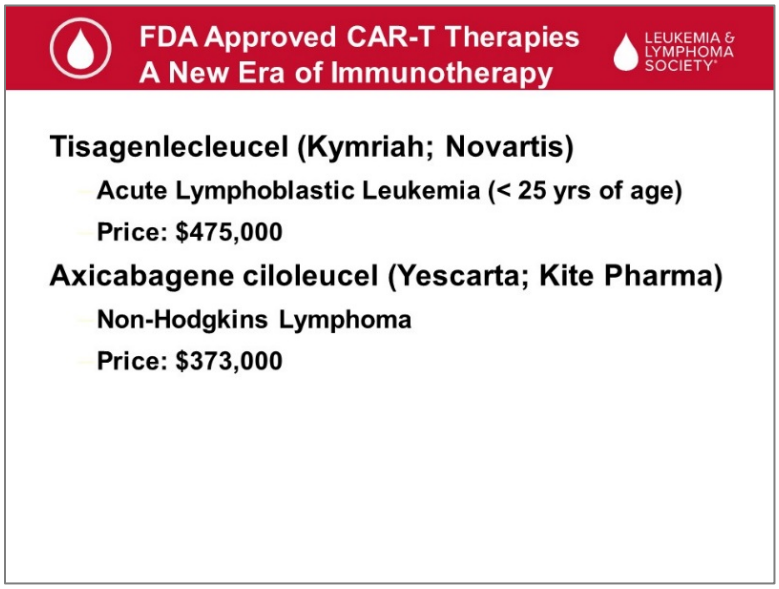


And so, they compared VMP with or without daratumumab (dara) and found that the responses were significantly better and deeper when they added the daratumumab upfront. Also, the molecular remission rate went up from 6% with VMP to 22% with the dara-VMP, so really nice responses.



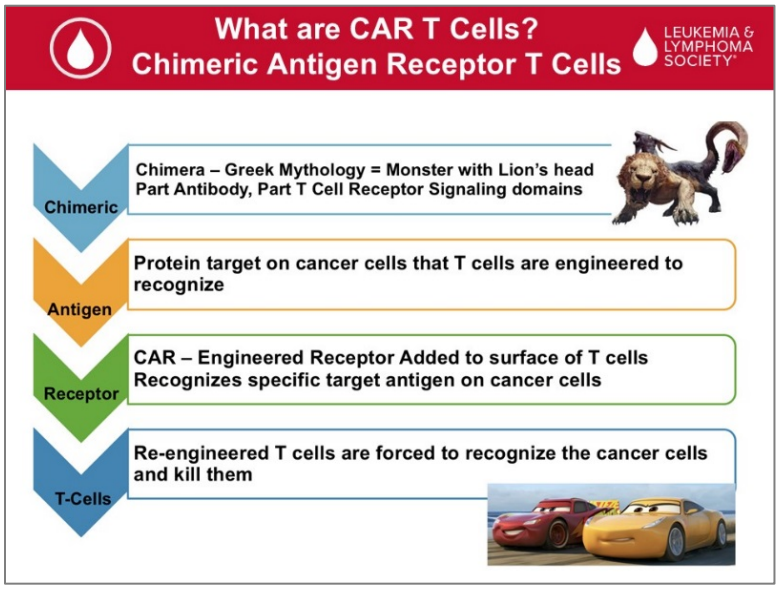
And, also, progression-free survival is significantly improved. And based on these data, it's actually approved not only in Spain, but also FDA approved for use in the US as upfront therapy along with melphalan-prednisone and Velcade, although we don't really use a lot of melphalan-Velcade combination upfront in the US, so we're not exactly sure that this is very useful yet. We tend to avoid melphalan in most patients upfront because it is stem cell toxic and precludes the use of stem cell

transplant later on because of poor ability to collect stem cells. And so, most patients we try to avoid that. And even in the elderly patients that are not able to go to transplant, we have data with really good results with other less toxic therapies like lenalidomide as well. And so, not really sure how this is going to be incorporated yet here in the US, but, hopefully, the other studies will show that it's also beneficial with other combinations.

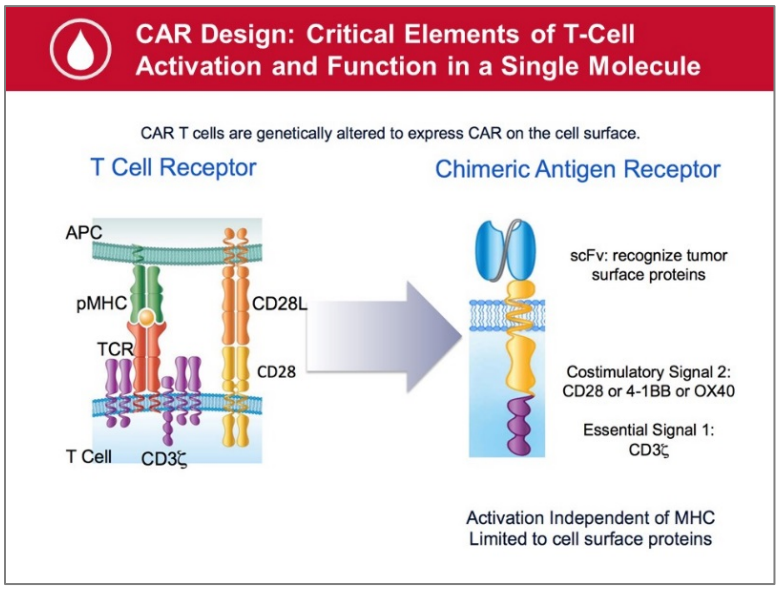


Okay, so we talked about the current therapies. What about the experimental therapies?

One of the most talked about therapies for blood cancers in general right now is referred to as CAR (chimeric antigen receptor) T-cell therapy. I'll have a couple of slides in a minute on what that means, but, essentially, it's a gene modified T cell. And we have studies in myeloma, but it's already FDA approved for use in acute lymphoblastic leukemia (ALL) for children under 25 and, also, for relapsed large-cell lymphoma. You'll notice that there's a hefty price tag that comes with these, but those two are already FDA approved. These two target CD19, which is a marker on most lymphocytes but not on myeloma cells.

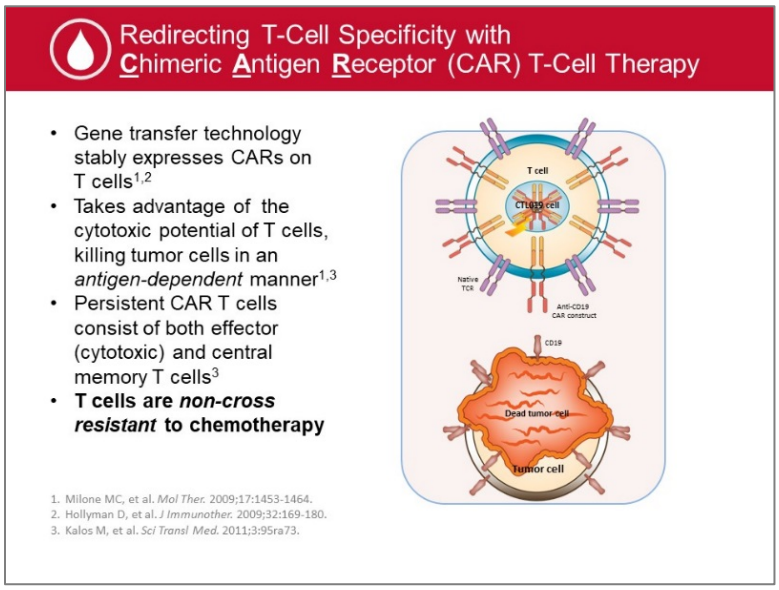


So, what does CAR T mean? So, C or chimeric. Chimera means monster in the Greek mythology that has the head of a lion and the body of a different monster. And, essentially, we have the head of an antibody on the outside of the molecule and the tail of the T-cell receptor, which I'll show you in a moment., so that's where they get the chimera. Antigen receptor is essentially a receptor on the cell that targets an antigen on the tumor cell. And these are T-cells. They're part of our immune system that fight either virus-infected cells or, in this case, tumor cells.

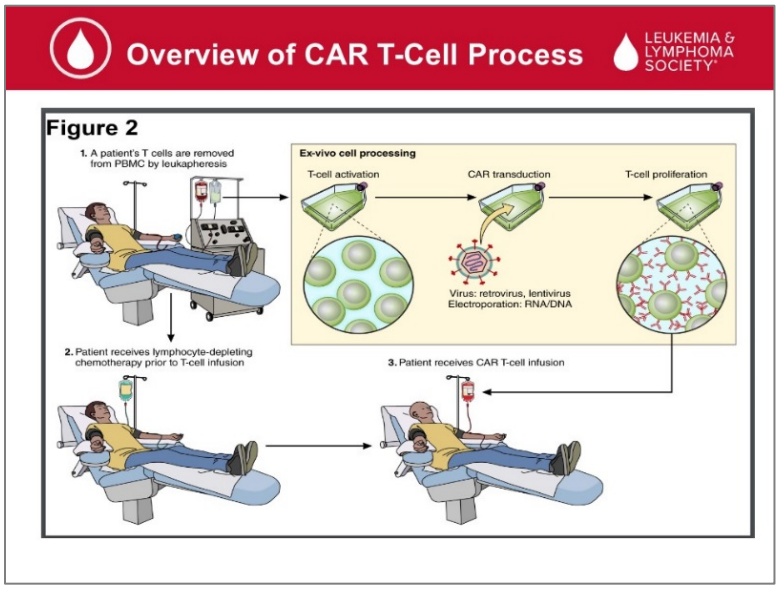


So, on the left, you see the normal T-cell receptor that's very complicated and recognizes target antigens as a little tiny peptide in the groove of a different molecule called major histocompatibility complex or MHC. So, it requires that the tumor express MHC, that they present that certain peptide and they have to have costimulation with a separate pathway like CD28. Whereas in the chimeric

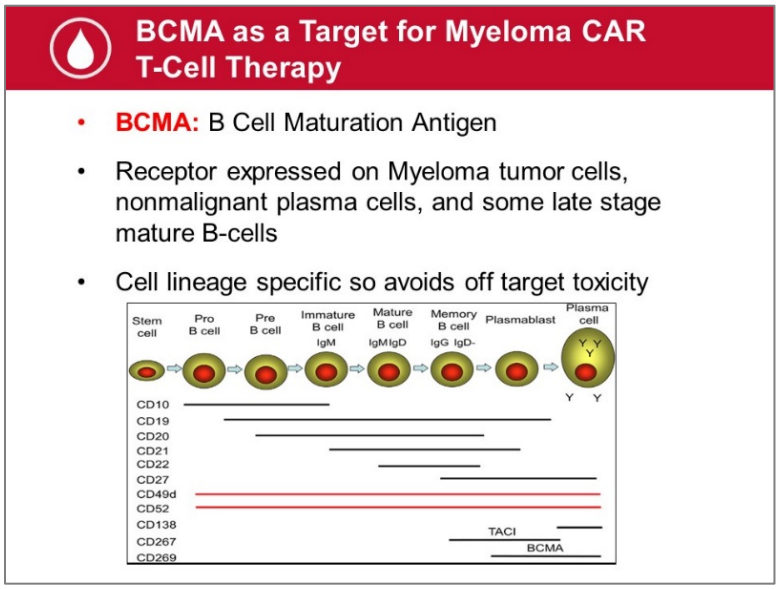
antigen receptor, we don't need an MHC on the target. We bypass that by having the business end of monoclonal antibody targeting the antigen on the outside of the cell. And then on the inside, we also link it with a costimulatory signal like CD28 or 4-1BB, so we don't have to rely on the T cell seeing that second signal on the tumor. And then it has the T-cell signaling pathway as well built in, so three different molecules all in one.



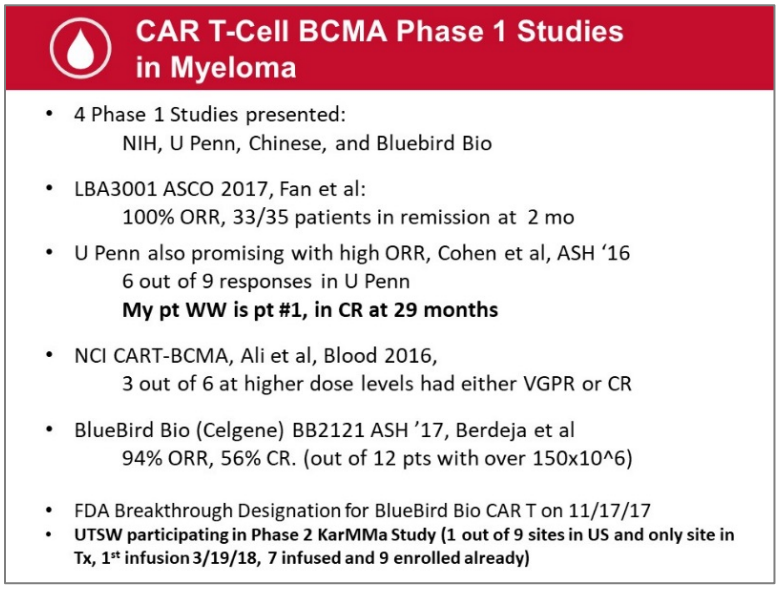
So, let's say we have a gene that we want to put in these T cells to make them become a CAR T cell. Right now, most of these are done with a virus that inserts this gene, this chimeric antigen receptor gene, into the T cells into the DNA. And then that DNA is then expressed and translated in a protein that goes under the surface of the T cells. And then those T cells can then go and attack the cancer and kill them. And the nice thing about these immune therapies is they're not dependent on response to chemotherapy. Patients could be resistant to all sorts of different treatments and still potentially respond to this type of treatment.



What does that look like for the patient? We have to first collect the T-cells. It's an apheresis collection machine much like we use for stem cell collection, but we don't have to give any growth factors to get them ready for it. We just hook them up to the machine through a catheter. And after a few hours, we've collected enough T-cells to send off to one of the companies making the CAR T cells. They get expanded with different molecules in the lab to grow up several million of these cells. And while they're growing, they get the gene inserted with a virus. The virus does not replicate. It's not able to survive. It just inserts its gene and then dies. And then it takes anywhere from three to six weeks to make these T cells, depending on the company and the study. And while the patient is getting ready to receive the T cells, they generally receive something called lymphodepleting chemotherapy with some fludarabine and Cytoxan to help get rid of some of their normal T cells and make space for these new CAR T cells that are getting infused in. So, they go through three days of lymphodepleting chemo, two days of rest, and then they get their CAR T-cell infusion on day zero.



But in myeloma, the commercially available products for CAR T recognize CD19, which is not expressed on myeloma. So, in myeloma, most of the studies are looking at a different target antigen called BCMA or B-cell maturation antigen, which is a marker specific for plasma cells and late-stage B cells. So, it's not on most normal B cells, just the later ones and the plasma cells. But it's not tumor specific. It's also a normal plasma cell.

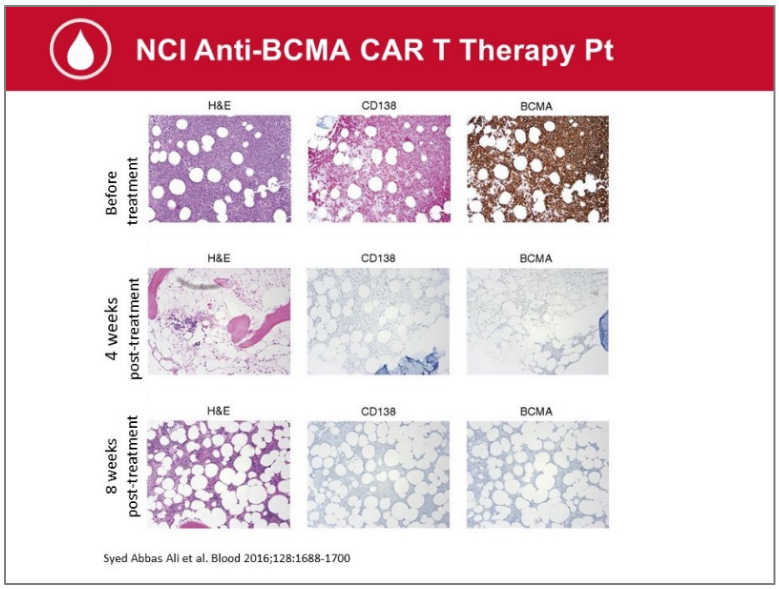


Four different phase I studies have been presented in meetings. So, the NIH (National Institutes of Health) has a variety that's been presented, the University of Pennsylvania, in China there's been a study that's been done and presented. And then, the fourth one is a company called Bluebird Bio that's in partnership with Celgene has presented their data as well.

The Chinese study showed essentially 100% response rate in a little over 30 patients at two months, so, very encouraging. University of Pennsylvania reported on nine patients that had received a reasonable dose of these T cells, and six out of nine had nice responses. And, actually, I'm taking care of patient number one who went to Pennsylvania to get this therapy. And I can verify that he had failed over 12 lines of therapy over the course of nine years for his myeloma and really had no options when he went there in 2015. And now, I should update the slide, I just saw him this week, he's now 31 months out from treatment and still in a complete remission with no signs of myeloma and no treatment since then, since November of 2015.

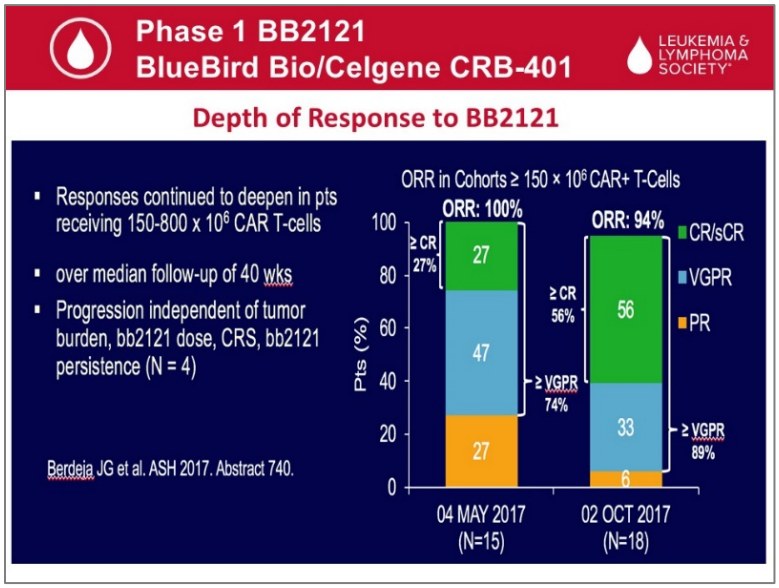
So, this is what is giving many of us hope and encouraging results that we're hoping that these treatments could potentially be a cure. We can't say that he's cured or that we don't [know] what percentage of patients will stay in these nice, longer remissions, but at least it can be very effective, even in heavily relapsed patients.

The NCI or NIH has reported on six patients and half of those had a deep remission. And then the Bluebird Bio partnering with Celgene has presented data on patients showing a 94% response rate and 56% complete remissions out of 12 patients who received over 150 million cells. Based on this data, it led to FDA breakthrough designation for the Bluebird Bio CAR T-cell product and now they've expanded to a phase II registration study. There are nine sites in the US participating in this phase II study, and we're fortunate to be able to participate here at UT Southwestern. We started on our infusions back in March and have enrolled nine patients. We, obviously, aren't reporting any data on these patients yet.

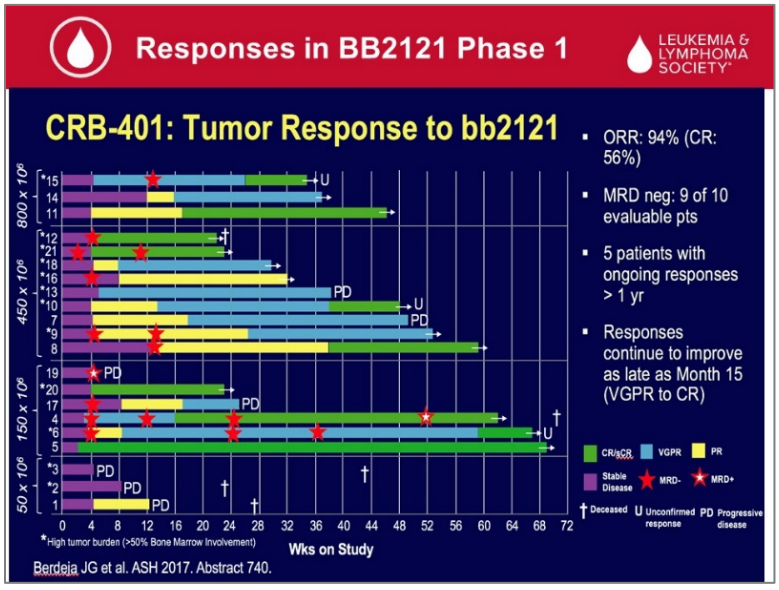


This is just an example of one of the patients in the National Cancer Institute (NCI) study of CAR T-cell therapy. The top bone marrow slide show that the bone marrow was packed with cells and stains for CD138. And BCMA confirmed that it's packed with myeloma. Four weeks after the CAR T-cell infusion, there's a few normal cells in there but no plasma cells or myeloma. Even eight weeks

later, the bone marrow was filled in with normal cells but no plasma cells. So, it's very striking and the bone marrow can be cleared even within two weeks in many cases.

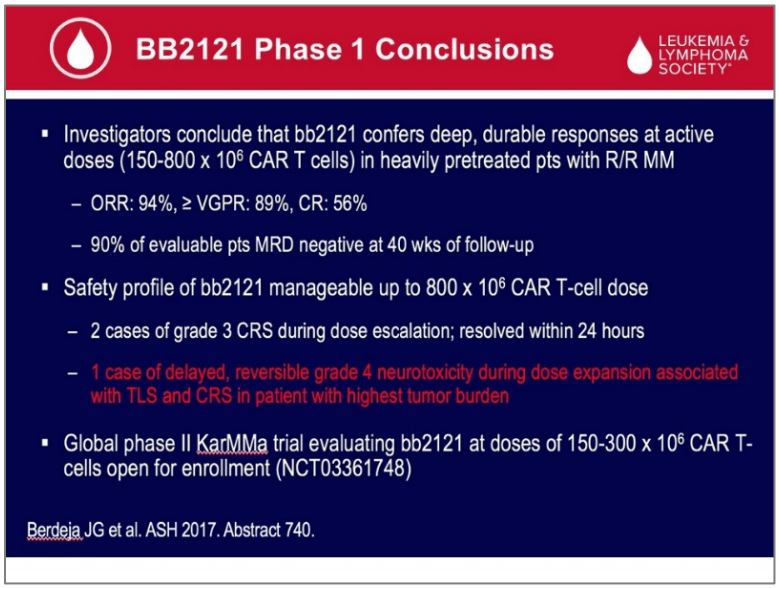


So, the Bluebird Bio study I mentioned the results, but this is just in graphical format. In May 2017, that data was presented at ASCO (American Society of Clinical Oncology). And then the October 2017 data was presented at ASH (American Society of Hematology) this past December showing that 94% of these patients achieved remission, 56% a deep remission.



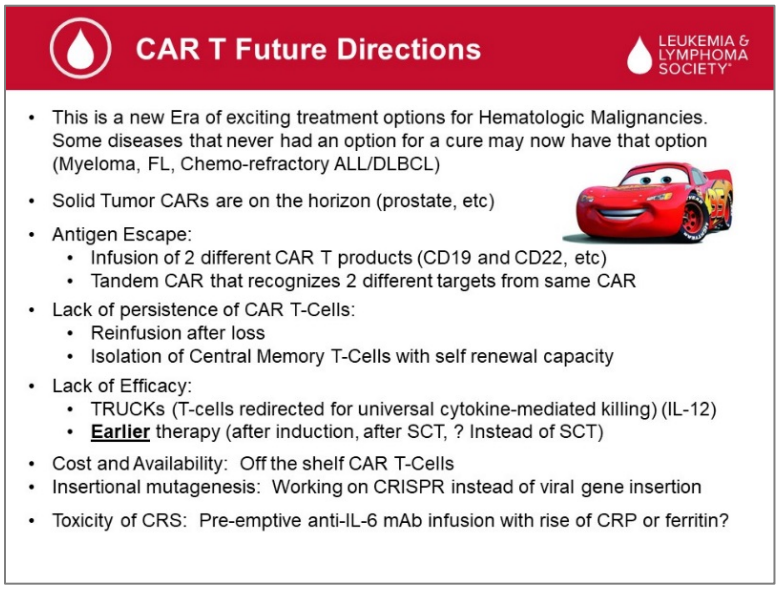
And if you look at all of the different patients and doses, you'll see that the patients that received the 50 million cells did not respond, but anything 150 or higher led to response in a majority of patients. So, with the phase II study, the company chose to go with 150 to 300 million. At the 450 and higher

million doses, they did see more toxicity with something called cytokine release syndrome where these T cells attack the myeloma and they release cytokines like interleukin-6 that can blow up and cause all sorts of fevers and low blood pressure. And at the high doses, they did have two cases of higher grade cytokine release syndrome and one patient that had some brain bleeding, although that patient was treated with steroids and is doing fine at this point.



But because of these potential side effects, even though this is very targeted therapy, it's not a walk in the park for every patient. We are requiring that these patients on trials for myeloma remain in the hospital for two full weeks after their CAR T-cell infusion to watch for this cytokine release syndrome, to watch for neurologic side effects. And then, after their two weeks in the hospital, they're required to stay within 30 minutes of the medical center for another two weeks. So, a whole month away from home if you're from out of state. And then, at the one-month mark, we'll do a restaging and determine how well it worked, and they can potentially come back for monthly visits at that point.

So, the phase II study that we're participating in is called the KarMMA study, and we're hoping it potentially leads to FDA approval in the next year or so, but the jury is still out.



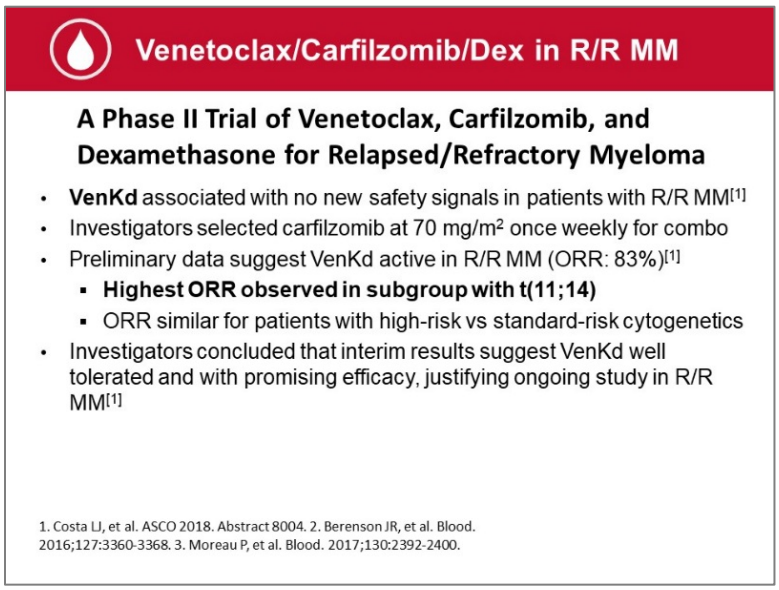
What other future directions do we have going in CAR T-cell therapy? These treatments do appear very effective, but I don't have a slide on this, but at ASCO a week or so ago, there was some data presented that some of these patients in molecular remissions after CAR T-cell therapy are starting to relapse. And so, we may have to find other ways of making these CAR T-cells more effective not only in myeloma, but we could, hopefully, start using these in many different cancers, including solid tumors like prostate cancer, etc. So, hopefully, this will have wide applicability.

One of the problems that we've seen in the leukemia and lymphoma patients is they can stop expressing the target antigen like CD19. And so, we might be able to overcome that by targeting two different antigens with two different CAR T-cells. What if the T cells don't stay in the patient? What if they all die off because they're what we call terminally differentiated and spent T cells essentially? One option that some groups are looking at are isolating memory T cells so that they have self-renewal capacity and less likely they all die off.

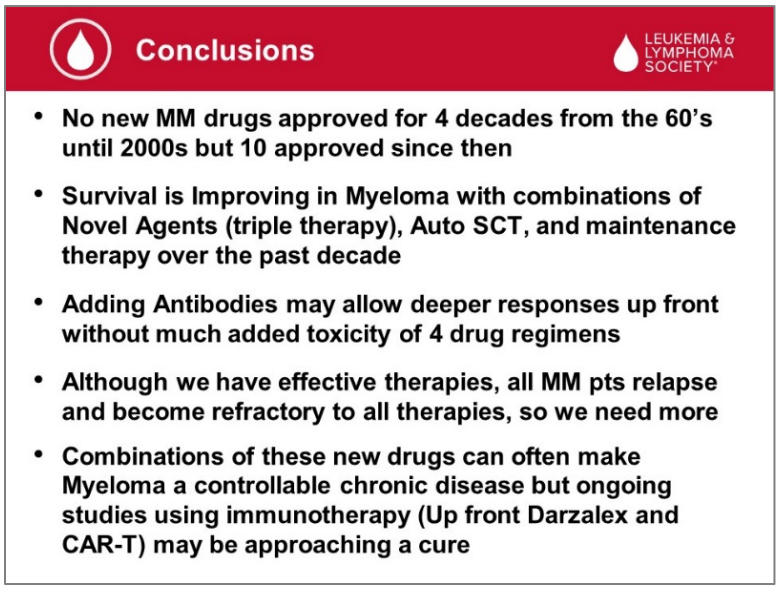
If the CARs don't work, we also have TRUCKs coming, which stands for T cells redirected for universal cytokine-mediated killing that secretes cytokines and help the other T cells stay alive.

One of the things that I think may be important is actually moving these therapies earlier in the course of disease. Instead of waiting until the patient's falling off the rails and failed every option known to man, what if we did this in first or second relapse and the patient's T cells may be in better shape? The patient may be in better shape. So future trials, hopefully this Fall, will be starting to address this. Certainly, the cost could be an issue, so others are working on what we call off-the-shelf CAR T-cells where we have sort of like MHC matched or HLA (human leukocyte antigen) matched donors that have donated and made CAR T-cells that can then be matched to the patient and then infused in. Also, these viruses that insert the gene could theoretically insert somewhere we don't want and cause trouble and so others are working on a nonviral-mediated transfer.

And then, as far as the toxicity, a quarter of these patients end up in the ICU and requiring intensive care. What if we follow their markers and look for signs that this is developing and give them preemptive therapy instead of waiting until they're in the ICU? So that's another thing people are looking at.

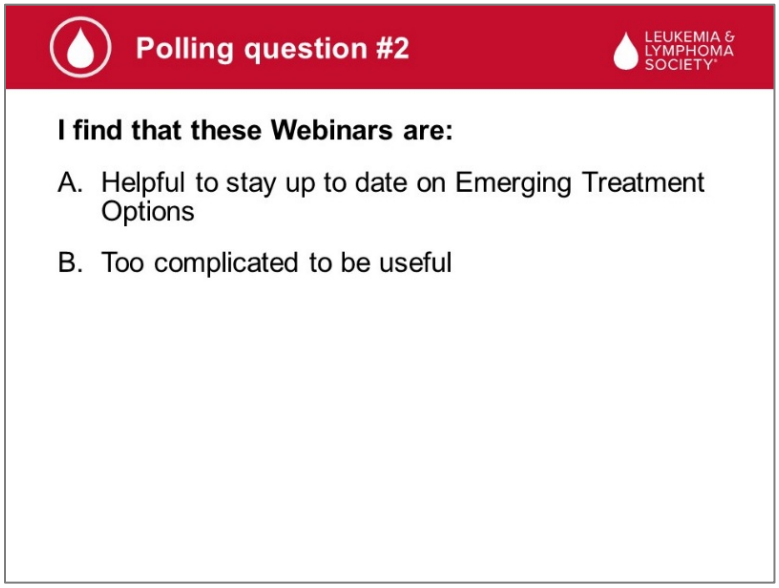


Other things on the horizon, one of the up and coming drugs that's been recently presented at ASCO is a drug called venetoclax. It targets BCL2. And now they've combined it with carfilzomib and dexamethasone for triple therapy. And even in these patients that are heavily refractory, they're seeing 83% response rates. And, in particular with the group of patients that have a chromosomal translocation in 11 and 14 chromosomes, we're seeing even higher response rates. So, this drug appears very promising.



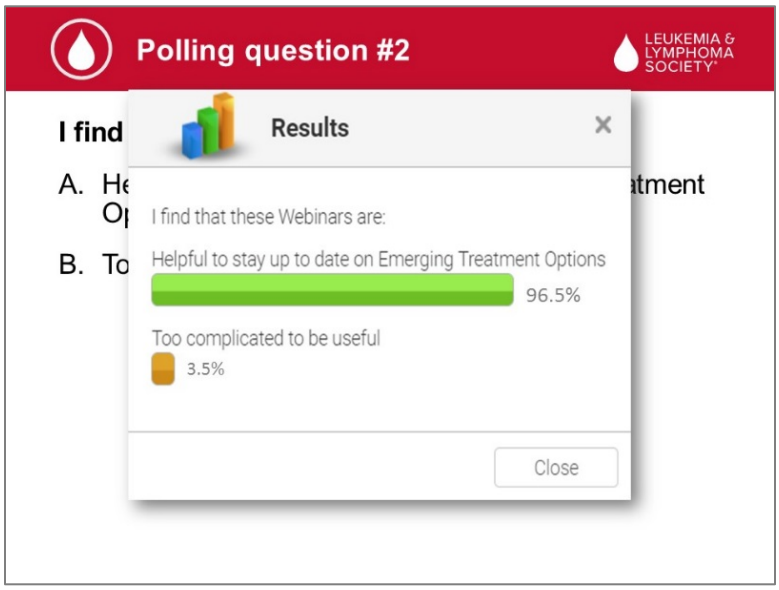
In conclusion, we saw no drugs approved from the ‘60s until 2000 for myeloma, but since then we’ve had at least ten drugs approved. The survival in myeloma continues to improve based, in part, by induction therapy with triple therapies; based on, in part, the stem cell transplant; based on maintenance therapy; and then also because of the effective relapse therapies that we have. Part of this is the monoclonal antibodies that we have now that are allowing deeper responses, but most of that data on the survival was before we had daratumumab. And so, we’re hoping that that will even further lead to improvements in survival. And then maybe even moving it upfront could make changes as well.

But, even with all of these effective therapies for myeloma, ultimately, almost all patients will still become refractory to all of them. And so, hopefully, we’ll find newer therapies, such as the CAR T or perhaps different combinations, that can help future generations of myeloma patients make this at least a chronic controllable disease like diabetes or hypertension, even if we can’t say that we’ve cured it.



Just wanted to get another quick poll and just to see with these webinars if patients (A) find it helpful to stay up to date with these things, or (B) with all the alphabet soup that we have in myeloma, is it too complicated to be useful?

Lizette Figueroa-Rivera, MA



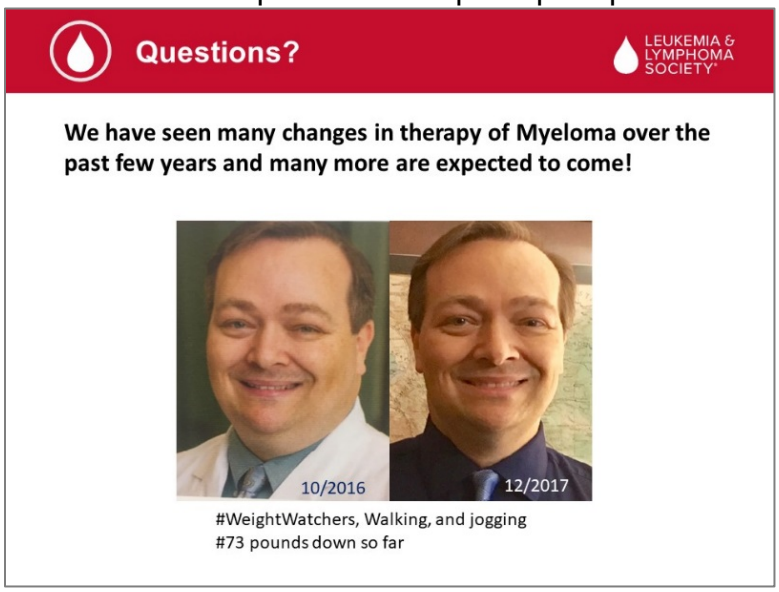
96.5% find it helpful to stay up to date on emerging treatment options and 3.5% find it too complicated to be useful.

Larry D. Anderson, Jr, MD, PhD

Okay, wonderful. So, 96.5% found it effective, but, certainly, we'll have to work on the other 3% and figure out other ways, too. But, certainly, it's encouraging that these things are helpful to many patients.

So, yeah, we've had a lot of improvements in myeloma. Certainly, more coming.

And I think at this point we will open up to questions.

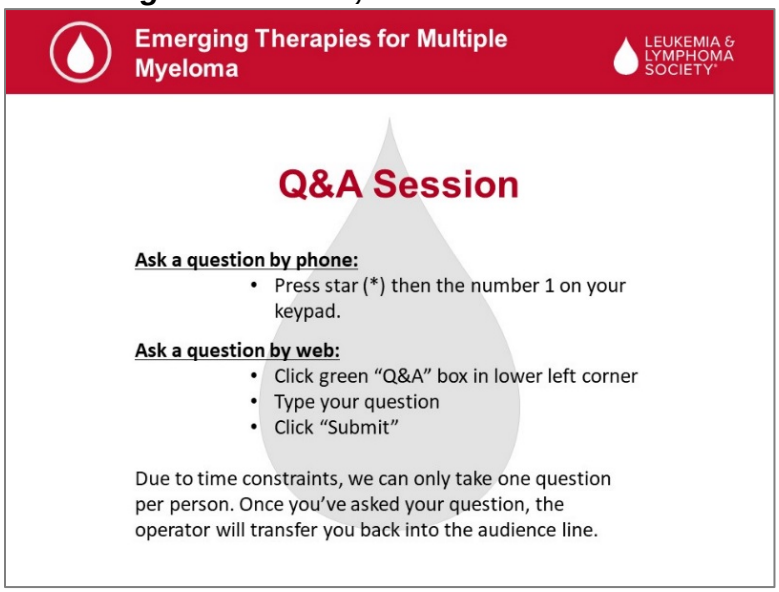


Lizette Figueroa-Rivera, MA

Sure. Thank you so much, Dr. Anderson, for your very clear and informative presentation.

QUESTION-AND-ANSWER SESSION

Lizette Figueroa-Rivera, MA



It's now time for the Question-and-Answer portion of our program.

We'll take the first question from the Web audience. Doctor, Richard asks, "On five-year survival graphs, how much of the improvements in longevity are explained by earlier diagnosis rather than better treatments?"

Larry D. Anderson, Jr, MD, PhD

Yes, so great question. So, is it the treatment that's improving, is it earlier diagnosis? I think there's some of both. You know, we are starting to catch patients earlier; and we know with smoldering myeloma, we have to watch them closely. But I think most of it is the better treatments. We just have so many better treatments these days, and that's also allowing us to start treatment earlier in some of these patients because of these more effective treatments with much less side effects than the treatments we had in the '60 and even '80s.

Lizette Figueroa-Rivera, MA

Thank you. And the next question, doctor, comes from the Web. It's from Paul. Paul asks, "If you become refractory to one drug class, for example, an IMiD, are you also refractory to all the other drugs in that class?"

Larry D. Anderson, Jr, MD, PhD

Great question. That is not the case. If you're refractory to one drug in a class, many times you can still have a nice response to other drugs in that same class. For example, patients that are refractory

to lenalidomide, about a third of them respond to pomalidomide, even though it's the same class. Patients that are refractory to Velcade may still respond to carfilzomib.

Generally, we don't go back to the earlier generation of this same class though. We go to the later generation. And, also, along with that, even if you're refractory to a certain drug, you may still have benefit from that drug when it's combined with a different therapy. So, you get something called synergy or synergistic activity.

So, for example, some patients may be refractory to pomalidomide and refractory to daratumumab, but then when you combine them together, about 30% of patients may respond to the combination. So, it gets very tricky on deciding these regimens and what the patient can and can't have. But, certainly, if you're completely failing one class, it doesn't hurt to change classes to maximize your benefit; but, certainly, you can still respond to something in the same class.

Lizette Figueroa-Rivera, MA

Thank you, doctor. And the next question comes from the telephone audience please.

Operator

Our next call is from Ralph from California. Please state your question. Your line is now live.

Ralph, from California

Hi, I've got a question. Is there any chance that you can trick the cells so that rather than the cancerous cell responding to an immune irritant, that a different cell would respond, therefore avoiding the expansion or the clonal expansion that you might have?

Larry D. Anderson, Jr, MD, PhD

So, basically, can we trick the T-cells are cloning. Are you talking about with the CAR T-cell therapy?

Ralph, from California

Or a different type of thing where the errant B-cells, if you could get a different one to respond, like a subclone that would have responded instead of the tumorous cell.

Larry D. Anderson, Jr, MD, PhD

Well, the problem is with the tumor cells, they're growing not necessarily in response to any reaction to something. They're just growing because their DNA has mutated, and it signals to keep growing. And so, you know, in the CAR T-cell therapy, we're expanding the T-cells to fight them and attack them. But, yeah, there's not really anything that's in the patient that's triggering those myeloma cells to keep growing that we know of. They're just growing on their own basically.

Lizette Figueroa-Rivera, MA

Thank you, and we'll take the next question from the Web. Doctor, Robert states that "today it will be 40 days since his wife's stem cell transplant. What could be done to help bring back her appetite and sense of taste? We know it's a slow process, but some help here would be greatly appreciated."

Larry D. Anderson, Jr, MD, PhD

Yeah, so after stem cell transplant, it's common to have some low appetite and queasiness and taste abnormalities for anywhere from a few weeks to a few months. It will come back, but there's not really a specific thing you can do to speed it up other than basically getting calorie supplements—Boost®, Ensure®—those kind of things, to make sure you're getting the calories in the meanwhile and just further time. Certainly, there are some appetite stimulants if you're really unable to get much down, but, generally, it's just a matter of hopefully just a couple more weeks it'll start to improve.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Camilla from South Carolina. Please state your question. Your line is now open.

Camilla, from South Carolina

Yes, I and my nephew also have myeloma. Is it a genetic thing?

Larry D. Anderson, Jr, MD, PhD

Good question. So, most patients with myeloma, it does not appear to be genetic in that most of them don't have family members with myeloma. We do have a couple families, some rare families that do have myeloma that seems to be some sort of genetic link, so I can't say never. There are some families. Most likely it's just something that you both got, you know, over your lifetime developed and probably not genetic. But, certainly, if more than two family members come down with it, one may want to do some chromosome testing to see if other families could be affected. But there's not really a specific test to look for a genetic predisposition to myeloma.

Lizette Figueroa-Rivera, MA

Thank you, and the next question from the Web is from Marian. "How to reduce fatigue in maintenance therapy."

Larry D. Anderson, Jr, MD, PhD

Yeah, that's a great question. So, reducing fatigue in maintenance therapy. So, one of the things that I do is, even though the FDA label offers continuous therapy, I typically give patients a week off after each cycle, so three weeks on and one week off, to give them a little bit of a break and improve that fatigue going forward each cycle. Also, if it's really bad fatigue, then dose reduction from 10 to 5 milligrams would be an option.

Unfortunately, we can't always completely get rid of the fatigue. It is something that could still be there. It's really just managing the dose if it's really unmanageable fatigue though.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Judith from Ohio. Please state your question. Your line is now live.

Judith, from Ohio

I heard the doctor say that you couldn't have a stem cell transplant if you were 75 and older. Is that right?

Larry D. Anderson, Jr, MD, PhD

So, the question is can you have a transplant if you're 75 or over? It depends on the center where you're treated. There's not a hard and fast age cutoff, other than I think Medicare probably wouldn't ever consider anyone over 80. Most centers would transplant up until the age of around 75 in the US. Now I've transplanted a couple 76-year-olds, and I think there's maybe a couple 78 at other centers.

Generally, I recommend stopping at 75 since we have so many other treatments; and, certainly, as we age, the side effects may become more intense with these things and harder to, and not as fast to overcome them. But it really depends on the physiologic age and how functional and how many other diseases does the patient have and how well they're doing. It's still something that could be considered at 75 or 76, and it also depends on how well the myeloma has responded and how good of a remission you're in as to whether or not it's worth taking that risk at that age. In Europe, I believe, they don't transplant over 65, so it depends on where you are.

Lizette Figueroa-Rivera, MA

Thank you. And our next question comes from Lynette. Lynette asks if the CAR T-cell is a cost per treatment or to get the patient to remission.

Larry D. Anderson, Jr, MD, PhD

Yes, my understanding is that the CAR T cost is for that one infusion, essentially the production cost with the several weeks of production and genetic manipulation and growth and everything to get that frozen product shipped back to the site, whether or not it works. But that's controversial and something that's up for debate. Should we only have to pay if it works? Right now, it's just for that infusion though.

Lizette Figueroa-Rivera, MA

And we do have a lot of questions asking about the projected approval timeline for CAR T regimens for myeloma.

Larry D. Anderson, Jr, MD, PhD

And I guess that's the half a million-dollar question in myeloma. I don't know the answer to that, but I'm hoping sometime in 2019. The earlier the better, but I don't have a crystal ball on exactly how fast the FDA will work on this. And we have to finish this current phase II study that's ongoing right now, which will probably take most of the rest of this year, and then they can start submitting it for early next year. So, hopefully, by mid-next year, but I can't guarantee that.

Lizette Figueroa-Rivera, MA

Sure, thank you. And we'll take the next question from our telephone audience please.

Operator

Our next call is from Richard from New Jersey. Please state your question. Your line is now live.

Richard, from New Jersey

Good morning, I've been successful. I've been in remission now three times over the last ten years, and recently I had daratumumab, the Darzalex® treatment, and it was very successful. Right now, I have no M spike observed at all; and I suggest to everybody out there, don't give up the fight. Hang in there. Take all the treatments, try clinical trials, do whatever you've got to do; but keep yourself alive.

Larry D. Anderson, Jr, MD, PhD

Wonderful.

Richard from New Jersey

That's about it, doc.

Larry D. Anderson, Jr, MD, PhD

I appreciate your input. Yes, so daratumumab definitely can work really well in many patients.

Lizette Figueroa-Rivera, MA

Thank you so much for your call and your comments. Our next question comes from Evelyn. Evelyn is asking, "If a patient is found MRD-negative, so that's minimal residual disease-negative, do you think maintenance therapy should be discontinued or continue for an extended period? Also, if continued, should that be at a decreased dose and/or dosing schedule?"

Larry D. Anderson, Jr, MD, PhD

So, the question's about what to do when we have MRD-negative or molecular remission. Can we stop maintenance or reduce it? The short answer is we don't know. We don't have any data yet. But studies are ongoing to help address this. In the meanwhile, it certainly depends on a lot of factors. If the patient is MRD-negative or molecular remission and having any side effects from maintenance therapy, that might be an option to say, "Okay, I'm having too much fatigue or too much diarrhea or something like that." Okay, at least it might be an option then to stop it.

Right now, we don't have data saying that those patients will do just as well stopping it, and others are proposing that we actually do the opposite and say, "Okay, only the patients that are positive we'll adjust the maintenance and intensify it." But studies are ongoing and planned to really help address this.

Lizette Figueroa-Rivera, MA

Thank you. And we do have Virginia as well as Marilyn asking what could be done about neuropathy.

Larry D. Anderson, Jr, MD, PhD

Yes, so neuropathy, I would say the best thing to do about neuropathy is preventing it in the first place by dose modification of the treatments like bortezomib while you're first getting the symptoms of it to help prevent it from getting severe in the first place. But let's say it is already severe, certainly, we have a lot of effective treatments to help with the neuropathy pain, like gabapentin, Lyrica® (pregabalin), Cymbalta® (duloxetine). All of those, really, just kind of mask the pain though. They don't really get rid of the neuropathy. They just make it bearable.

And so, we can often get patients a much better quality of life with these medications and then just further time. Two-thirds of the patients, actually, closer to three-fourths of the patients, will have significant improvement of their neuropathy over time. That can be anywhere from a couple months to a couple of years. Sometimes it can be much more drawn out.

In the meanwhile, there is some data on acupuncture that can help with neuropathy in those that aren't getting benefit from the other methods. But mostly it's just time and then medicines to help with the pain.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Larry from Wisconsin. Please state your question. Your line is now live.

Larry, from Wisconsin

Yes, I'm on Revlimid, and the doctor that I see here in Madison doesn't mention anything about any other drugs to take. But I'm in remission, but I was just wondering why doesn't the government step in and start making the prices more reasonable for people that don't have insurance? Twenty-one pills for $15,000 seems pretty ridiculous.

Larry D. Anderson, Jr, MD, PhD

Yes, it is a big problem with the cost of all of these treatments; and especially when you start combining the treatments that are each $10,000 or $20,000 a month. Many are advocating right now and lobbying Congress and government to try to regulate the cost of these medicines; and many people higher up than me are working on that. But, unfortunately, right now most of us don't really have a say in it; but, hopefully, that will change in the coming years.

Lizette Figueroa-Rivera, MA

Thank you. And here at LLS, we are advocating for patients on the Hill, so hopefully you, as well as others on this call, will join our advocacy efforts.

Our next question is from Ira. Ira asks, "How long or how many circles of treatment should a patient stay in a current treatment if progress is not met before his oncologist decides to change the treatment plan?"

Larry D. Anderson, Jr, MD, PhD

Okay, so how long should you stay on a treatment if it's not working? So, it really depends on, let's say you have relapsed myeloma or newly diagnosed, and you're on treatment and it stabilized the disease that was rapidly progressing before, that could still be of benefit. And so, if it's at least stabilizing things, you could consider staying on it.

But if the numbers are still going up, generally, I would say give it two to three cycles. But if it's, certainly, rapidly rising before then, after a cycle, then it really depends on how fast the numbers are

going up. But, generally, two or three cycles of something. And if it's not working, then consider moving on or combining it with something else.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Janezetta from Wisconsin. Your line is open. Please state your question.

Janezetta, from Wisconsin

Yes, is it true that only the people over 60 get this, and were we subject to some type of toxic or some type of- because I have very bad allergies, and everything triggers me. So, I was wondering if I caught this because I was exposed to chemicals or exposed to different things since I have very bad allergies.

Larry D. Anderson, Jr, MD, PhD

Most people don't have any known exposure that caused their myeloma. We don't know what causes myeloma. You know, certainly, there are a few things like Agent Orange and a couple other things. Maybe if you were a crop duster or something, but most people don't have any specific exposures they can think of.

And it's not just patients over 60. The average is in the 60s, but I've got patients in their 20s and 30s with myeloma. And, really, anything related to allergies would not be affecting the myeloma. It takes probably several different genetic mutations in that one clone, one plasma cell in the bone marrow over your lifetime. The main reason that most people are in their 60s is because it takes that long to develop all of those different mutations in that one plasma cell.

Lizette Figueroa-Rivera, MA

Thank you. And our next question comes from Patricia. Patricia asks, "What do you suggest to support or protect the liver and kidneys while on long-term Revlimid-Ninlaro (ixazomib) and dex?"

Larry D. Anderson, Jr, MD, PhD

Yes, so to protect the liver and kidneys, so the main thing is stay hydrated; and most patients with myeloma, we try to avoid dehydration because your kidneys may be more sensitive. Avoiding intravenous contrast with CAT scans, unless it's really, absolutely required. Avoiding high doses of Tylenol® (acetaminophen), but generally, we don't have to do anything specific for the liver and kidneys on long-term maintenance. But avoiding a lot of nonsteroidals like Advil® and Ibuprofen, those kind of things, in myeloma is also a good thing.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Elizabeth from Massachusetts. Please state your question. Your line is now live.

Elizabeth, from Massachusetts

Hi, thank you very much. This is a great program! I'm wondering, you haven't talked about the use of stem cell transplants for people who have already gone through the induction chemotherapy as well as the stem cell transplant and have been on the triple treatments basically of Rev-dex and Ninlaro. So, what's your opinion or are there any studies that relate to a second stem cell transplant?

Larry D. Anderson, Jr, MD, PhD

Yes, and just to clarify, you're talking about using a stem cell transplant, a second stem cell transplant to treat relapsed myeloma, right?

Elizabeth, from Massachusetts

Correct.

Larry D. Anderson, Jr, MD, PhD

Yes, so I didn't talk about it, but, certainly, there is data that it can be very effective. The criteria that we would use would be if a patient has had at least a year and, preferably, two or more years of remission after the first transplant, and then at relapse, we can certainly consider doing a second transplant. We try to collect enough stem cells for two upfront and have them frozen so that that is an option down the road. But the reason I didn't bring it up is we have so many other less toxic options now for relapse with Kyprolis and daratumumab and all of the other ones that it's really becoming more like a third- or fourth-line option and not something we would jump on right away, unless maybe the patient had a ten-year remission and really had never had anything in between. That's still something we would consider.

Lizette Figueroa-Rivera, MA

Thank you. And the next question comes from Diane. Diane asks, "Is there an injection-type medication that replaces the Pomalyst® (pomalidomide) pill?"

Larry D. Anderson, Jr, MD, PhD

Injection that replaces Pomalyst. So, the IMiDs, like thalidomide, Revlimid, and pomalidomide are all oral. There's not an IV version of that. The proteasome inhibitors come in either subcutaneous IV or oral. But, yeah, the IMiDs, there is no injectable form.

Lizette Figueroa-Rivera, MA

Thank you. And our last question today comes from Richard. Richard asks, "What is the latest on multiple myeloma remission?" I heard early on that the first remission is usually the longest. Is this still the case?

Larry D. Anderson, Jr, MD, PhD

So, we used to say that the first remission is the longest, and with each subsequent treatment or relapse that remissions keep getting shorter and shorter. But now we're challenging that because some of the current treatments we have for relapse, like monoclonal antibodies, are really effective. And so, it's very common to see much longer remissions with second- or third-line therapy. But every patient's different. So historically, yes, that was true; but I think we're seeing changes in that.

Lizette Figueroa-Rivera, MA

Thank you. Thank you, Richard, for that question which was the last of our questions today.

Thank you so much, Dr. Anderson, for your continued dedication to patients. You and your colleagues' research successes have really made such a positive impact on people's lives; and I just wanted to ask you what you're most excited about with all this research and everything coming up for myeloma.

Larry D. Anderson, Jr, MD, PhD

Yes, an honor to be here. Thank you so much for doing this, and I'm most excited about CAR T-cells and, more specifically, I think the upcoming trials where we'll be moving those up to second-line therapy and trying to get patients on these before they've exhausted all of their other options. I think it'll be even more effective.

Lizette Figueroa-Rivera, MA

Definitely, and we're very happy that we have so much going on in myeloma and in the last really five to ten years.

Larry D. Anderson, Jr, MD, PhD

Yes.

Lizette Figueroa-Rivera, MA

Great, thank you.

CLOSING REMARKS

Lizette Figueroa-Rivera, MA

And for our audience today, if you weren't able to get your question in, please contact The Leukemia & Lymphoma Society Information Specialists at 1-800-955-4572. Information Specialists are available to speak with you from 9 AM to 9 PM Eastern Time or you can reach us by email at infocenter@LLS.org. We can provide information about treatment, including clinical trials, or answer other questions you may have about support, including questions about financial assistance for treatments.

Please note that Continuing Education credit is not being offered for this program for professionals.

Again, we'd like to acknowledge and thank Amgen, Bristol-Myers Squibb, Celgene, and Takeda Oncology for support of this program.

And thank you, Dr. Anderson, for sharing your knowledge with us today.

To all the patients, caregivers, and professionals participating in today's program, on behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us.

Goodbye and we wish you well, and this program will be posted on our website at www.LLS.org/programs. Thank you.

Larry D. Anderson, Jr, MD, PhD

Thank you.