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. Craig Cole for sharing his time and expertise with us today. We have over 1,200 people participating in today's program and across the United States and several countries around the world, including Angola, Canada and India.

Before we begin, I'd like to introduce a member of The Leukemia & Lymphoma Society's National Board, Ms. Connie Lindsey, who will share a few words. Ms. Lindsey, please go ahead.

Connie L. Lindsey

Thank you, Lizette. Good morning, good afternoon and good evening. I'd like to add my welcome to the patients, caregivers and healthcare professionals attending our program today. The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer. For more than 60 years, LLS has helped pioneer innovation such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients.

My husband John is a multiple myeloma survivor diagnosed in 2005, so daily we express our gratitude for the work of The Leukemia & Lymphoma Society, and we're determined to continue to invest and actively support the work of The Society.

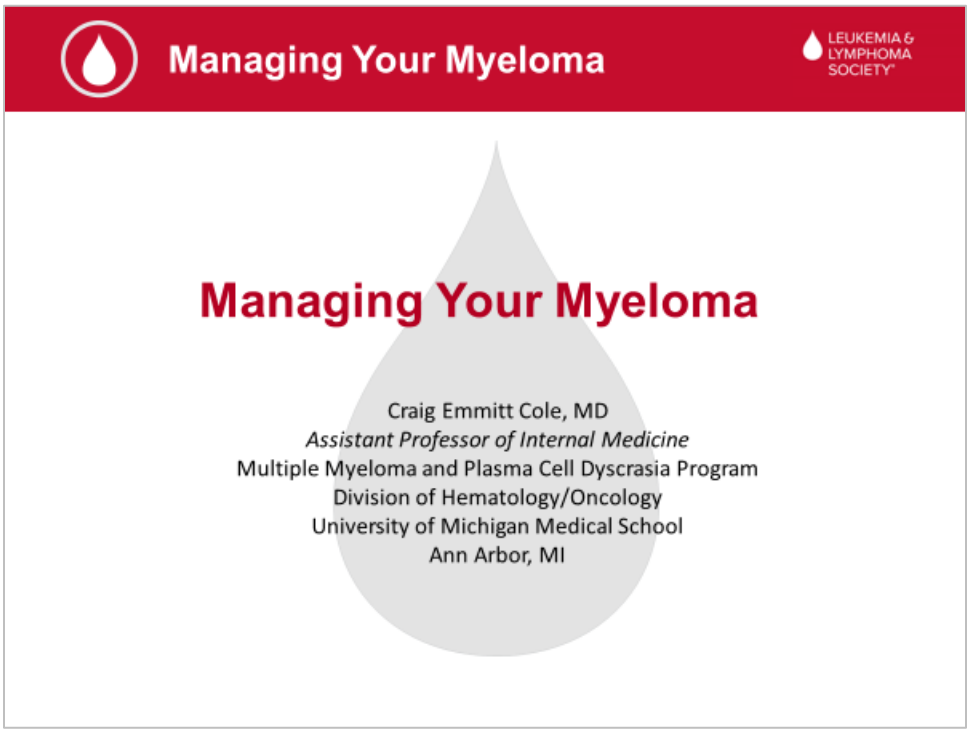
To date we've invested over $1 billion in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside. In addition, as this program demonstrates, we are the leading source of free blood cancer information, education and support; and we touch patients and their communities through our 56 chapters across the United States. 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 treatments and ensuring that they have access to quality, affordable and coordinated care.

We're fortunate to have as our presenter today Dr. Craig Emmitt Cole, one of the nation's leading experts in myeloma. We deeply appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. On behalf of LLS and all those we serve, I'd like to thank Dr. Cole for providing us today with important information on diagnosis and treatment options for myeloma patients.

Thank you once again, and now I'll turn the program back to Lizette.

Lizette Figueroa-Rivera, MA

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

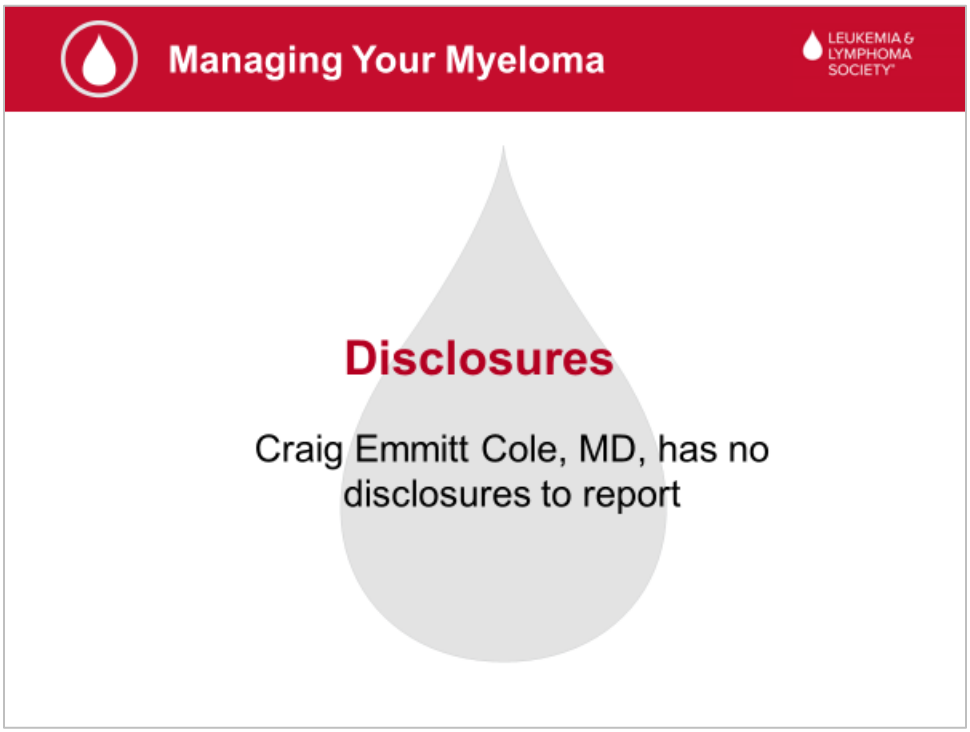


PRESENTATION

Lizette Figueroa-Rivera, MA

I am now pleased to introduce Dr. Craig Cole, Assistant Professor of Internal Medicine, Division of Hematology/Oncology at the University of Michigan Medical School in Ann Arbor, Michigan.

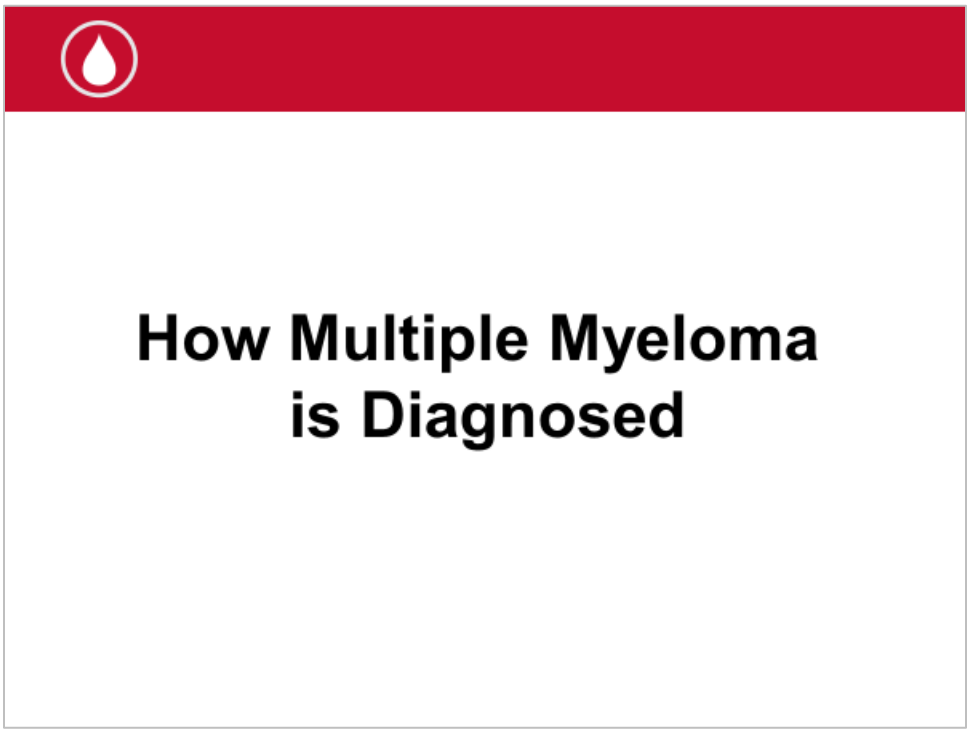
On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise with us. Dr. Cole, I'm now privileged to turn the program over to you.



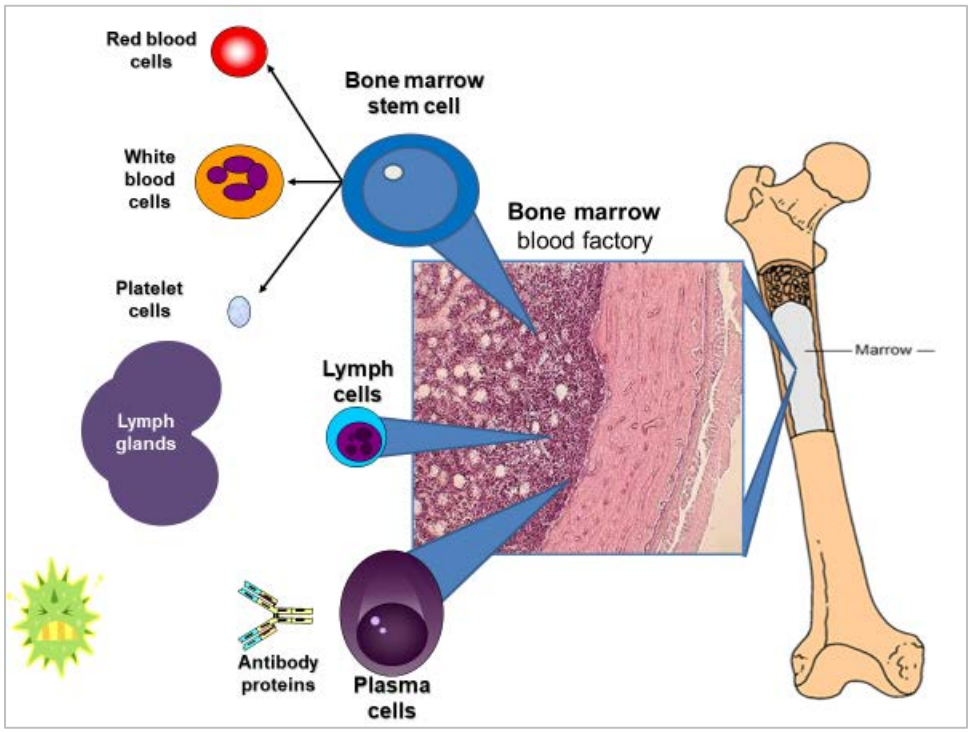
Craig Emmitt Cole, MD

Oh, thank you. Thanks for the very kind words, and especially thank you to The Leukemia & Lymphoma Society, who I've been working with for almost a decade now. It's really an honor to be invited to speak by such a great advocate for myeloma patients, for both research and an educational source. So, again, thanks for inviting me.

What we're going to talk about today is, first, how myeloma is diagnosed, the treatments for both newly diagnosed and relapsed myeloma, advances in the research in myeloma, which has really revolutionized this disease very quickly. And then because of all of the advances, it is now critical to have an excellent patient-physician communication in order to discuss all the treatment options that are available now.



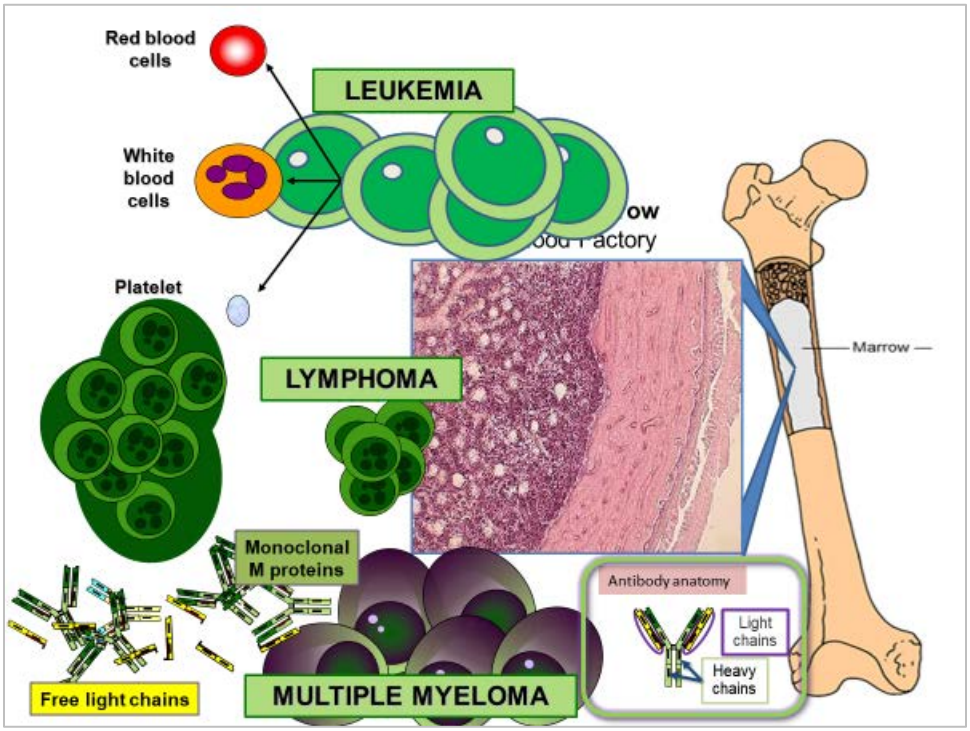
So how is myeloma diagnosed? And one thing that is, I think, really important for patients and caregivers with myeloma, is to be able to discuss their disease with their friends and family and other patients. Otherwise, you risk being isolated. If you can't describe the type of cancer you have, then it's tough to discuss that with family. And as a myeloma doctor, every time I go to Thanksgiving, they always ask me to look at their skin; and I tell them that I do myeloma, not melanoma, and then they have me look at their moles. And I say, "No, I do blood cancers and not skin cancers."



And here's a description that I give for the blood cancers and what is myeloma, and it takes just a little bit of anatomy and biology to discuss. So, inside the bones, there's the bone marrow; and the bone marrow is the squishy stuff that's in the middle of the screen in that slide. And inside the bone marrow is actually the blood factory, and there's stem cells in the bone marrow. And they make the red blood cells, white blood cells and the platelets that float in our blood on a regular basis to fight infection, make blood clots and deliver energy to our bodies.

There are also the lymphocytes that live inside the bone marrow, and they are part of the infantry that goes out and fights infection. They usually travel between the lymph nodes or the lymph glands and to the bone marrow to fight infection, and they travel back and forth to help us fight infection on site.

And then inside the bone marrow there are the plasma cells, and the plasma cells are more like the artillery. They remain in the bone marrow. They don't move out of the bone marrow normally, and they fire smart bombs or missiles or antibodies towards infections. And that's how they help to participate in fighting infection is by using antibodies.



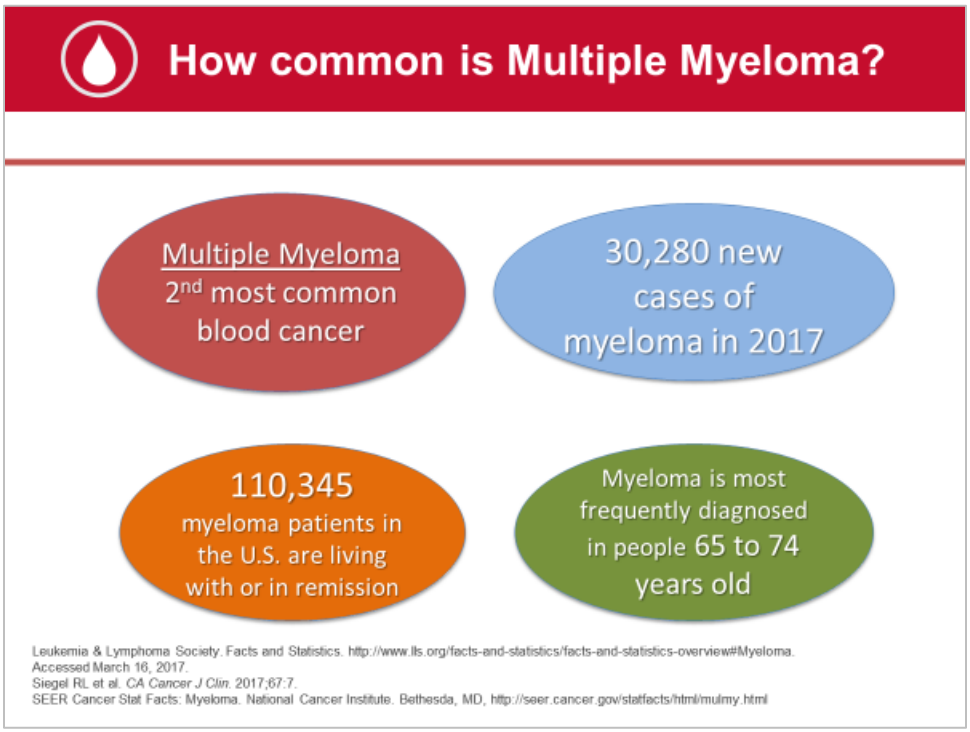
So as any cell in the body can turn cancerous, the cells inside the bone marrow can become cancerous; and when people have mutations in cancer of the stem cell, that's called leukemia. Those cells then grow inside the bone marrow and take over the space inside the bone marrow.

If the lymphocytes turn cancerous, that's called lymphoma, and they'll occupy space in the marrow; but also, they'll go to their other home, the lymph glands, and they'll expand and grow inside the lymph glands. And that's why patients with lymphoma will frequently present with enlarged lymph nodes as a sign of their disease.

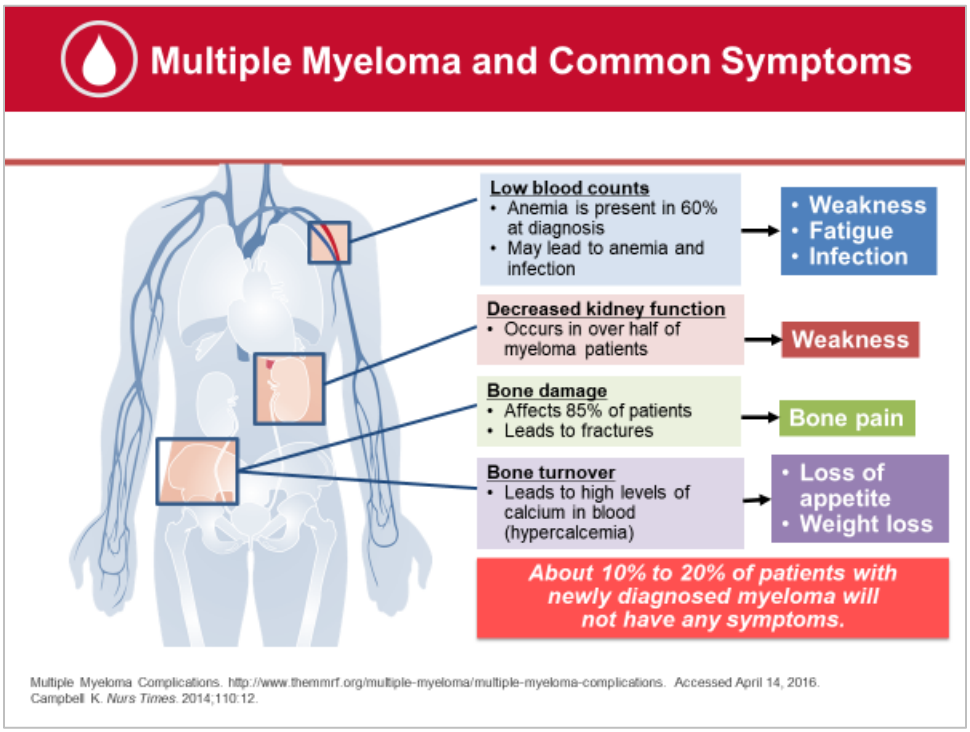
Myeloma, when the plasma cells turn cancerous inside the bone marrow, those cells remain inside the bone marrow and proliferate; and instead of going to the lymph nodes or anything like that, they remain inside the bone marrow, and they produce monoclonal proteins. Those monoclonal proteins have a stalk shaped like a Y that usually fight infection; but when they're mutated, they can't do anything. And that's called the heavy chain.

And then attached to those heavy chain stalk are the light chains. They're fragments of the antibody. And when the plasma cells turn cancerous, they make excessive numbers of just worthless antibody that can be detected in the blood and will be one of the first signs or tests to do to look for multiple myeloma.

And that's how I describe myeloma is to say that it's a cancer of the plasma cells that live in the bone marrow and can be detected and followed by a blood test looking for the protein that those cells produce.



So how common is multiple myeloma? Well, it's the second most common blood cancer. Lymphoma is number one. There are 30,000 new cases diagnosed with multiple myeloma last year; and, thank goodness, there are 110,000 people living with myeloma, and that number has been rising every single solitary year. And myeloma is most frequently diagnosed in people over the age of 65, and so it is not found in children.



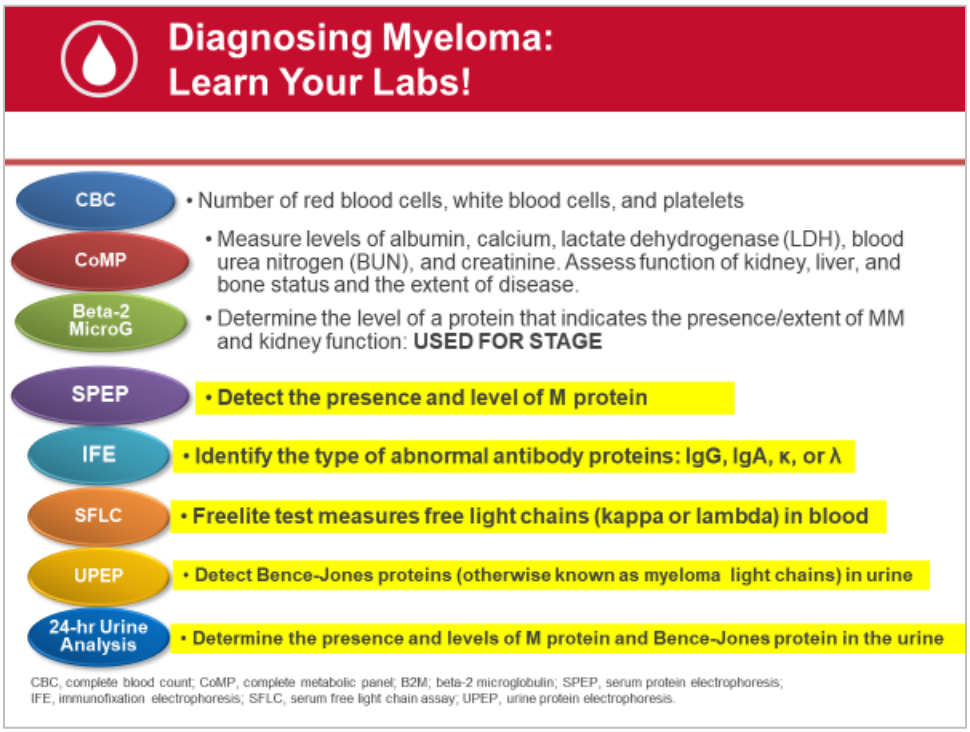
What symptoms, what problems do people present when they have myeloma? Well, a lot of patients will have low blood counts, especially low red blood counts, which is called anemia; and people will have fatigue and weakness, and they can be more susceptible to infection when they have low blood counts because the plasma cells are taking over the machinery of the bone marrow.

Patients can also, about half the patients, will present with decreased kidney function; and not so much the production of urine but more of the filtering of the blood plasma inside the kidney. And when those poisons and those chemicals that should be removed by the kidney aren't being removed because the kidneys aren't working well, then people have weakness and fatigue.

Most patients will have some type of bone damage because of myeloma. The plasma cells that live in the bone marrow will look for other places to reproduce and to proliferate, and those will be the bones; and it chews away at the bones, making the bones thin. And that can lead to fractures, bone pain and, again, weakness and fatigue.

And because the plasma cells go to the bones and they cause bone destruction, calcium is released from the bones; and it can cause high calcium levels, which, again, cause a weakness, fatigue and sometimes confusion.

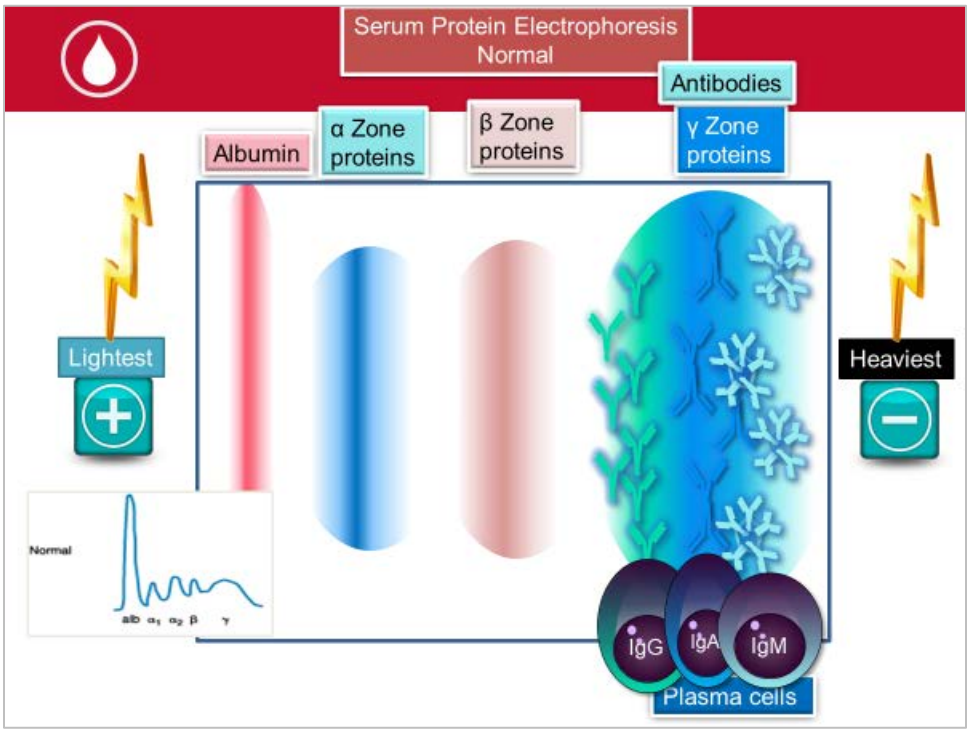
But about 20% of patients with myeloma will not have any symptoms, and their myeloma will be discovered using some other, a blood test, particularly one's looking for anemia or for excessive protein in the blood. And that number is actually rising also.



So what labs do we use to follow and diagnose myeloma, and myeloma is a lab-followed disease. It is important to know your labs. The first one is the complete blood cell count or the CBC (complete blood count) which measures the red blood cells, white blood cells and platelets, and especially the red blood cells which can cause anemia when they're low. Also, the comprehensive blood panel; that measures the electrolytes and especially the calcium which can go high. The creatinine or kidney function, liver function, and also the lactate dehydrogenase, the LDH, which we'll talk about in a little bit yet.

And then there's a blood test called the beta-2 microglobulin; and although we'll check the CBC and comprehensive panels on a regular basis to follow the course of the disease and the treatment, the beta-2 microglobulin is used only once or twice during the course of myeloma. It is exclusively used for staging purposes, and we'll talk about that in a bit.

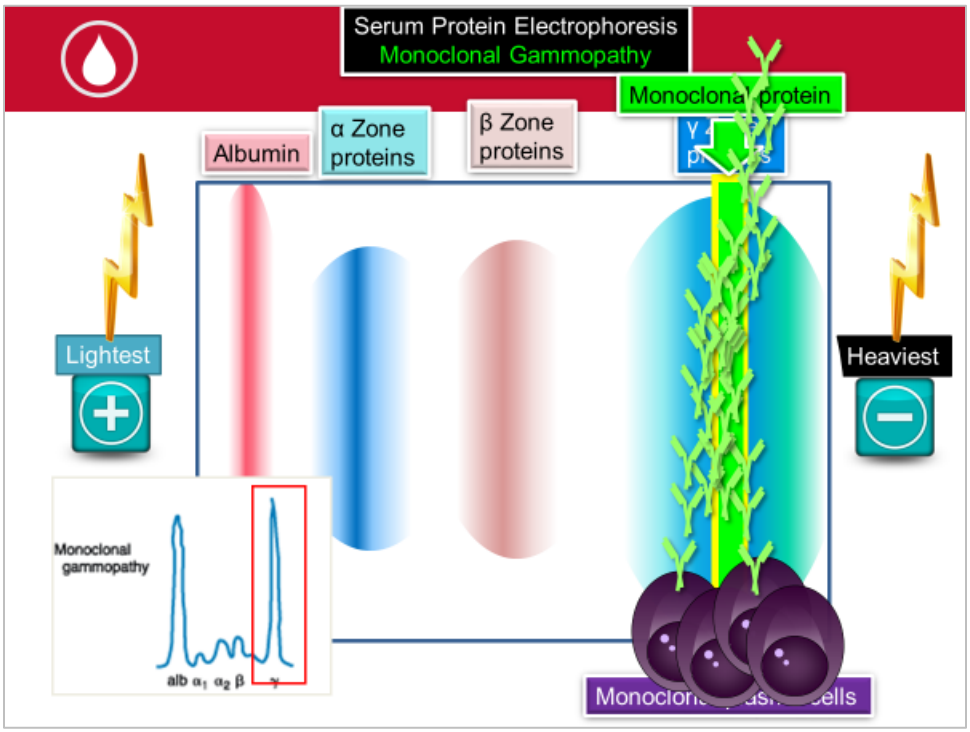
The blood tests that will help you tell what the disease is doing are in yellow. The SPEP (serum protein electrophoresis) is used to detect the level of M protein or the amount of monoclonal protein produced by the plasma cells. Immunofixation will tell you what type of antibody is being produced by the plasma cells: IgG, IgA, sometimes IgD, kappa or lambda. The free serum light chain test has been revolutionary in being able to tell the status of patients' disease with light chains only, instead of using the urine test. But we still have the UPEP (urine protein electrophoresis) test, the Bence-Jones test and the Bence-Jones quantitative test, the 24-hour urine test and we'll talk about that in a bit also. But those are the important labs that we follow when patients have myeloma.



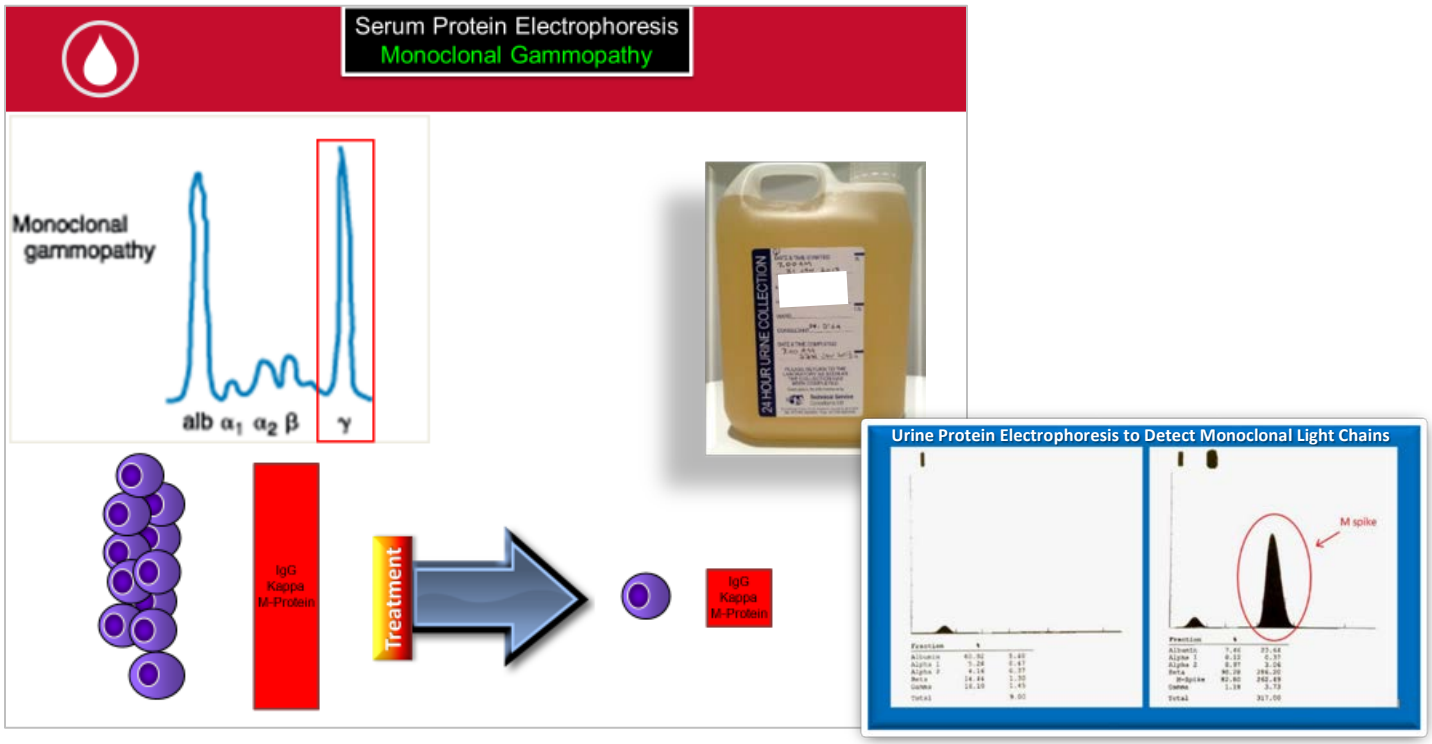
So, what is that protein electrophoresis test if it's so important? Well, it's done on a gel, and the blue-black is actually a gel. It's kind of thick like Jell-O, and there's an electrode put at each end of the gel. And what we do is we get some of the plasma from the blood test, and we put it in that gel and plasma is negatively charged. So, when we turn on the electricity inside the gel, the blood plasma will go through the gel; and actually, the proteins will segregate out by weight. The proteins that are the lightest will go all the way to the positive electrode, and the really heavy proteins will be stuck towards the negative electrodes. So, it separates the proteins out, and then we can analyze it.

Albumin is a very common protein, and it's one of the lightest proteins, so it's right next to the positive electrode. The alpha and beta proteins are other proteins like hormones and ferritin. And then at the very end is the gamma zone, and that's where the antibodies hang out, produced by the plasma cells. And IgM is probably the heaviest. IgA is the second lightest, and the IgG is the lightest one; and it bleeds a little bit over sometimes into the beta zone.

So that's what a normal SPEP or serum protein electrophoresis would look like, where there is a broad band of protein at the gamma area with all those different proteins being produced by the bone marrow in plasma cells.

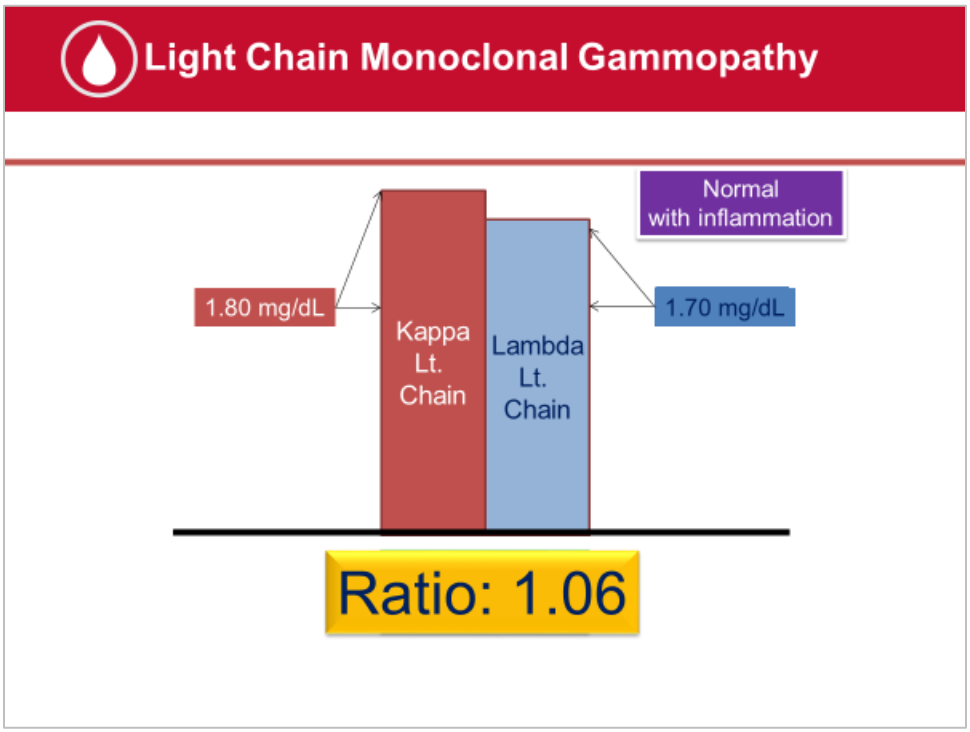


Now if someone has a monoclonal gammopathy, if they have myeloma or smoldering myeloma or MGUS (monoclonal gammopathy of unknown significance) when you do their protein electrophoresis test, actually the proteins will, again, segregate out by weight. But there'll be a band right in the middle of the gamma region, and that will be the monoclonal protein. That's the test that we use to follow the multiple myeloma or other plasma cell problems. And the reason that there's a single band is that all the plasma cells are all the same, as being part of a cancer, all the mutations, all the plasma cells are identical. They produce identical weight antibodies, and those identical weight antibodies stop right at the same region inside the gel, pile up on top of each other, and then we can count them and count the amount of protein in that area. And that gives us the number of what the M protein is.



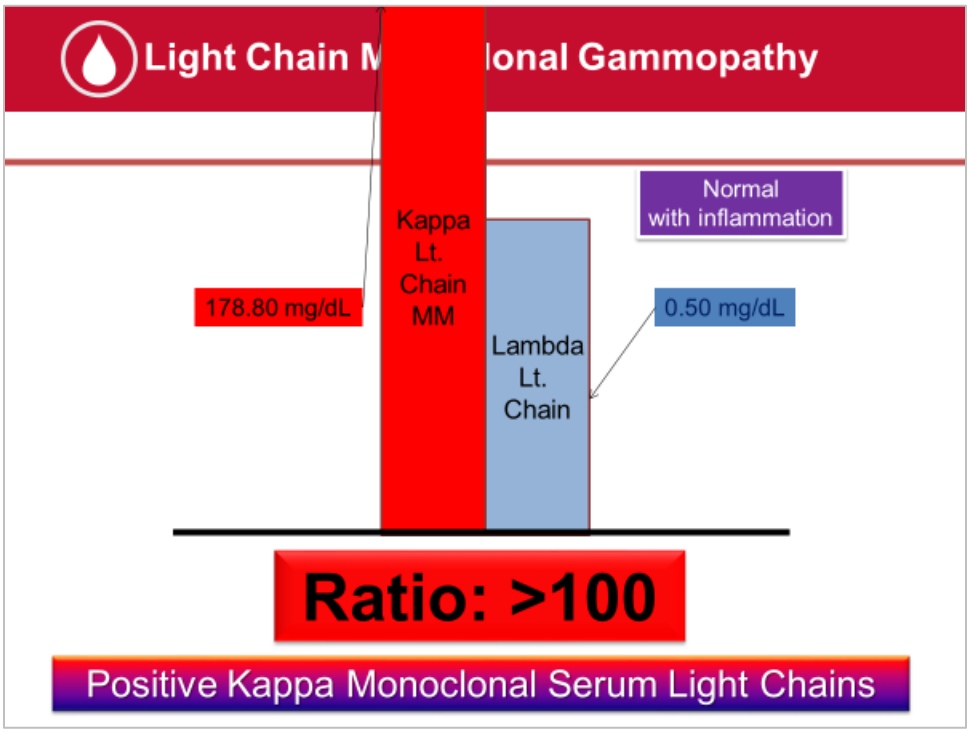
And the M protein is directly related to the number of plasma cells. So instead of doing bone marrow biopsies every month, which I'm sure no one would want us to do, we can check the M protein to see how the cancer's doing. So, at diagnosis we know what the protein level is. It can be like 5.3 grams, and the bone marrow can have 60% plasma cells. And when we do a treatment, what will happen is that the treatment will lower the amount of cancer cells; it'll kill the cancer cells, and it should lower the protein too. So, it's really important to know what your protein is because you want to know the treatment's working, and to tell how the treatment's working, we watch a decrease in their protein level.

But myeloma cells are tricky, and sometimes they'll produce those fragments of antibodies, the light chains; and the problem with the light chains is that when you turn on the electricity in the gel, those light chains will run right off the page because they're so light, they'll wiggle all the way through the gel, and it can't be seen. So, in order to detect the light chains, for the past 175 years, we've been doing urine testing to look for those light chains of multiple myeloma. And I'm sure everyone's familiar with the urine jug. That's not apple juice in there; that's urine. And we've been doing that for 175 years, the first test ever for cancer. And that will have an M spike just like the serum will when we analyze the urine.

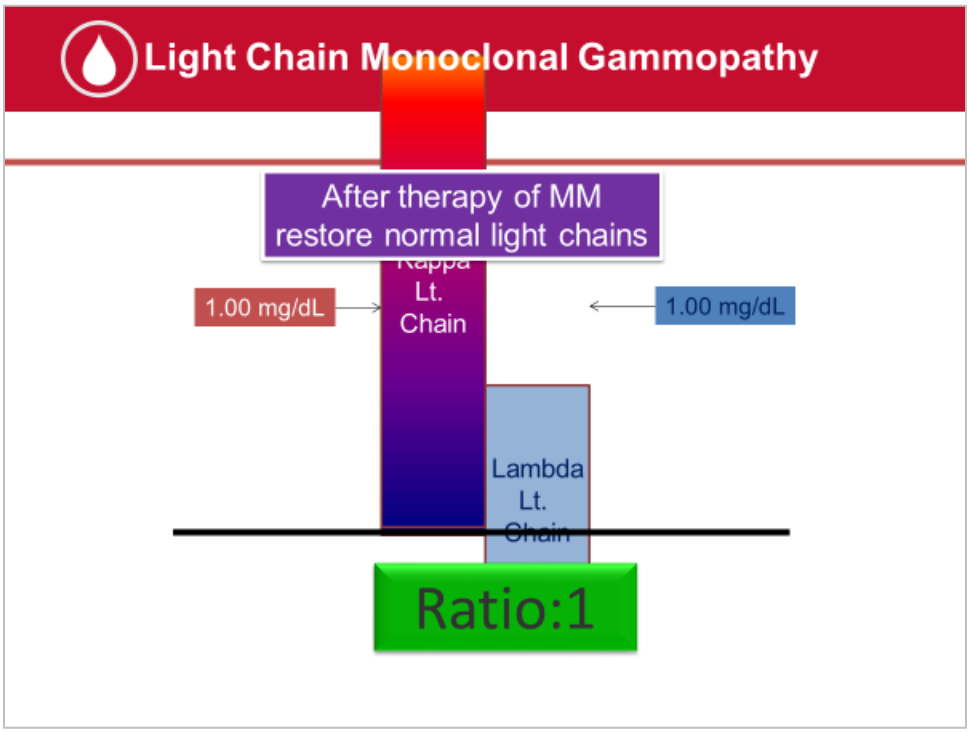


But patients wanted something else besides checking their urine every month. And so, what was discovered, with the help of LLS, is a serum light chain analysis. So instead of checking your urine, we can check your blood; and the blood test, when we check a normal person's immune system, we'll find traces of kappa and lambda, those light chains in the blood. And usually it's about 1 gram for each, and those go to fight infection.

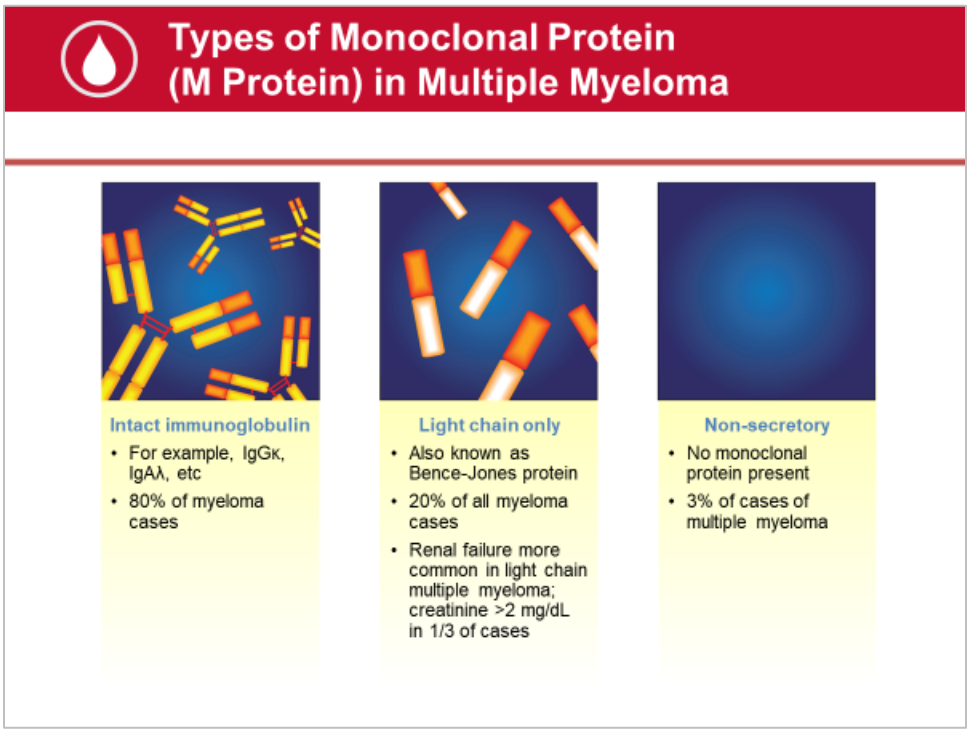
And if you have an infection, what will happen is that the light chains will go up in response to having an infection. So, if you have inflammation or infection, light chains go up. But still the ratio between the two should be normal, a 1:1 ratio.



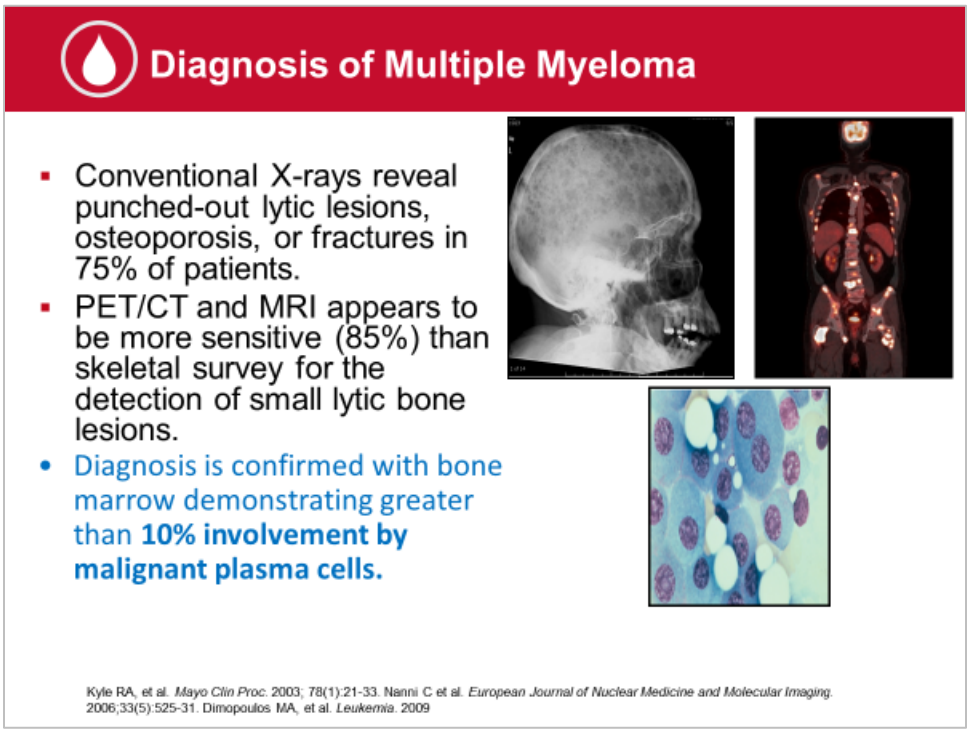
Now, if somebody has multiple myeloma or MGUS or any of the plasma cell disorders, they'll, just like with the heavy chains, they'll produce a light chain that will be very high, around 100 and something. And because those plasma cells are aggressive, they'll destroy the normal plasma cells; and the lambda will go down. And then the ratio is, of course, very skewed, over 100; and that's consistent with multiple myeloma.



And what we do is that we, just like with the M protein, when we use treatment for myeloma, we expect the kappa light chains to go down if those are the ones that are involved and the normal immune system to grow back; and then the ratio goes back to one. And that's one of the goals of treatment when we are treating myeloma is to bring down the protein which we know will bring down the number of plasma cells.



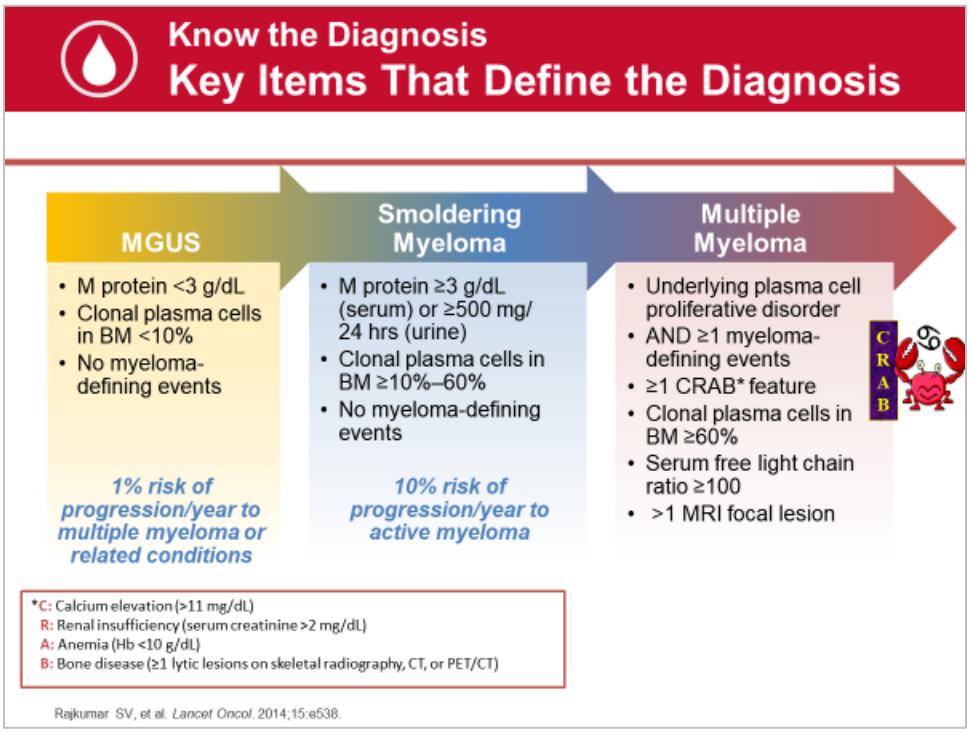
About 80% of patients will make an intact antibody that is found on the SPEP and IgG or IgM. About 20% of patients will only make light chains, so we need either urine tests or the free serum light chain test to monitor the disease; and renal dysfunction is frequent in most patients because the light chains get caught in the kidneys. And then there are a minority of patients where none of those tests work, and then we have to use x-rays and bone marrows to follow those types of myeloma.



So, for the past 117 years, we've been using x-rays to monitor and diagnosis myeloma; and patients with myeloma will have holes in their bones frequently or lytic lesions where the myeloma has chewed away at the bone because it needs bone in order to grow, just like in the bone marrow.

That test is 117 years old, and now we have new tests. The PET (positron emission tomography) scan and MRI (magnetic resonance imaging) are 85% more sensitive at picking up lytic lesions. In this PET scan that I'm showing, if you see the bones, all those little dots that light up are all areas of myeloma involvement; and some of those would not be seen by standard x-rays. So, the PET scan, whole body CT (computerized tomography) scan and MRI would be a very important test in the diagnosis of myeloma; and we still do x-rays because they're easy to do. But we'll frequently do PET scans and MRIs these days.

And, finally, the diagnosis is confirmed by doing a bone marrow biopsy; and a normal percent of plasma cells in the bone marrow is 1%. And if you have over 10%, then that's consistent with myeloma.

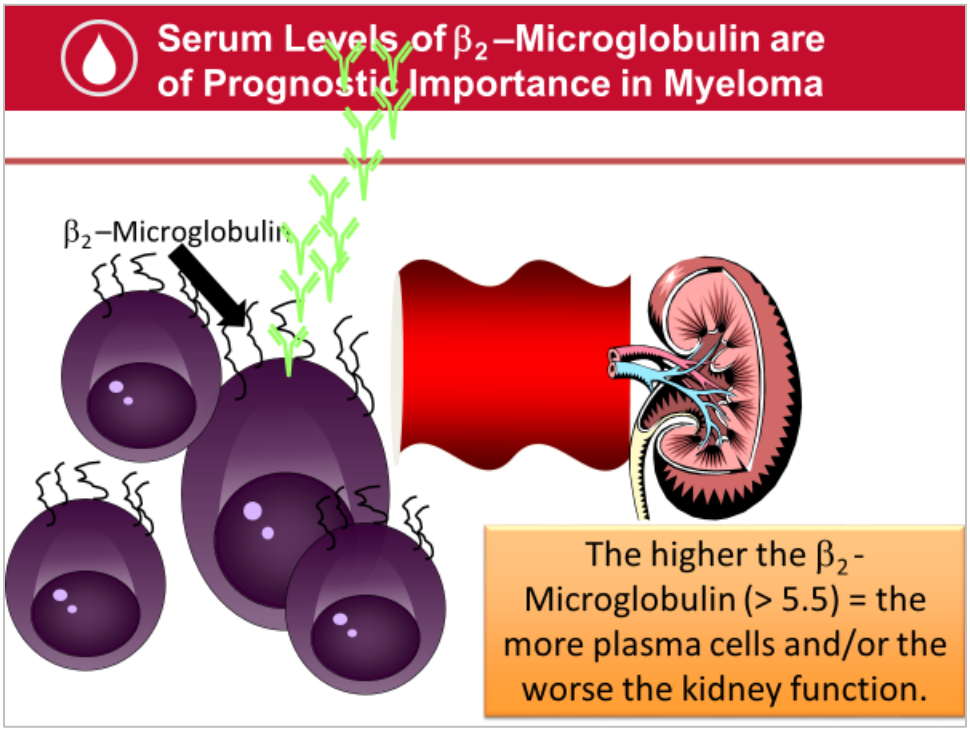


There are several different types of plasma cell disorders. The most common one is MGUS or monoclonal gammopathy of uncertain significance—very common, is not a cancer. Patients do not have symptoms. It rarely turns into multiple myeloma, and those patients will have less than 10% plasma cells in the bone marrow.

Then there is smoldering myeloma. So, some patients, a minority of patients with MGUS, will develop smoldering myeloma; and those patients have greater than 10% plasma cells in the bone marrow. Lots of protein because there's lots of plasma cells in the marrow; but those patients are asymptomatic. They have no symptoms, and they have a higher risk of turning into myeloma.

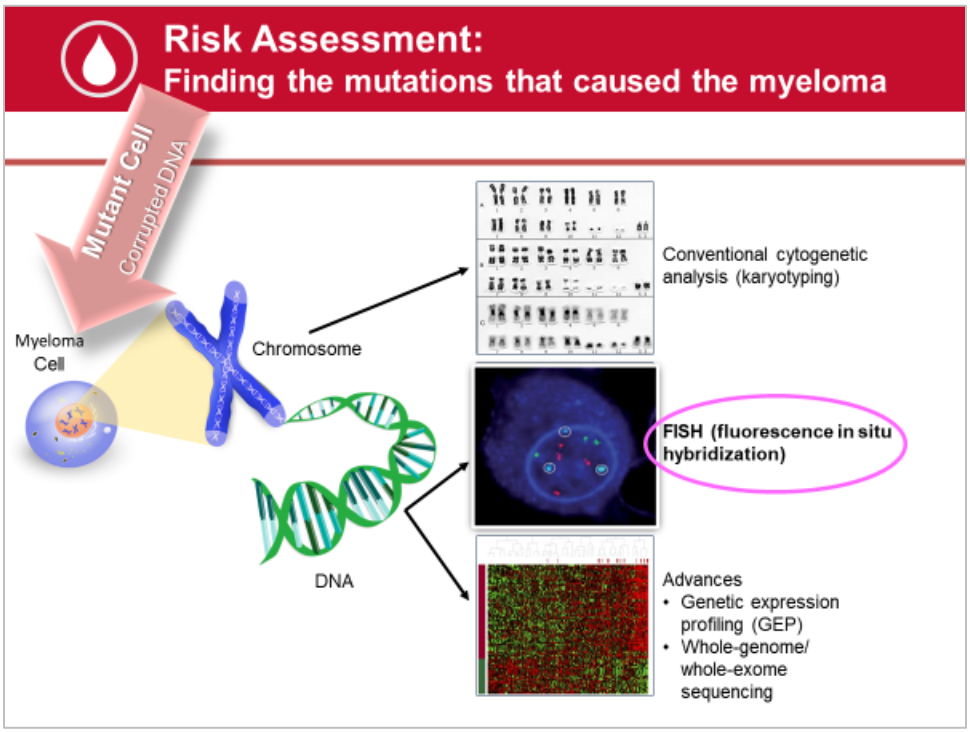
And then multiple myeloma is when you have greater than 10% plasma cells in the marrow, and you have one of the myeloma-defining events. And there is my little crabby guy. And CRAB is high calcium, renal insufficiency or kidney problems, anemia with a low hemoglobin and bone disease found by either x-rays, CT scans or PET scans.

If you have greater than 60% plasma cells in your bone marrow, that's one of the new criteria for myeloma or if the light chains are really high or if the MRI picks up a lesion. But usually it's a bone marrow biopsy plus one of the CRAB criteria defines myeloma. And all patients with myeloma start out at some point with MGUS.

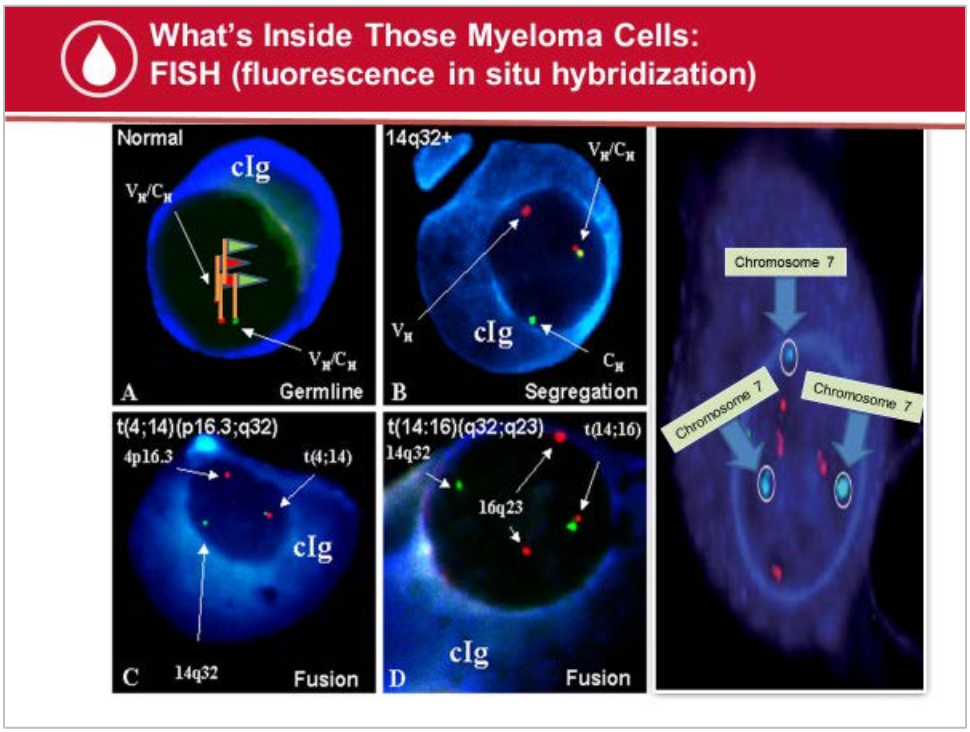


So how do we stage myeloma? Well, we've been using for several years the beta-2 microglobulin. I mentioned that blood test a bit earlier. The beta-2 microglobulin is kind of a nifty test. There are these little hairs that are on plasma cells that is called beta-2 microglobulin, and they're pretty standard in number, pretty fixed in number and they're on all the bad plasma cells. And because we can't really predict exactly how much M protein is made by each plasma cell, the beta-2 microglobulin is more of a stable result that we can check when staging how many plasma cells are in the body of the patient.

And the one thing about the beta-2 is that it is metabolized by the kidney; and the higher the beta-2 microglobulin will result in either telling us that there are lots of plasma cells present or that the kidneys don't work well. And worse kidney function is a prognostic factor in myeloma, as well as having a lot of plasma cells. And the beta-2 microglobulin gives us two prognostic features for the price of one test.



And the higher the beta-2, the higher the stage. One of the newer ways that we assess risk or how difficult the myeloma is to treat is by looking right at the plasma cell, looking at the mutations that corrupted DNA or chromosomes that are inside the plasma cells. So if the plasma cells mutate for some reason as we get older, it can turn into myeloma; and we can actually look at the mutations that occurred, especially by using the FISH test, the fluorescence in situ hybridization test.

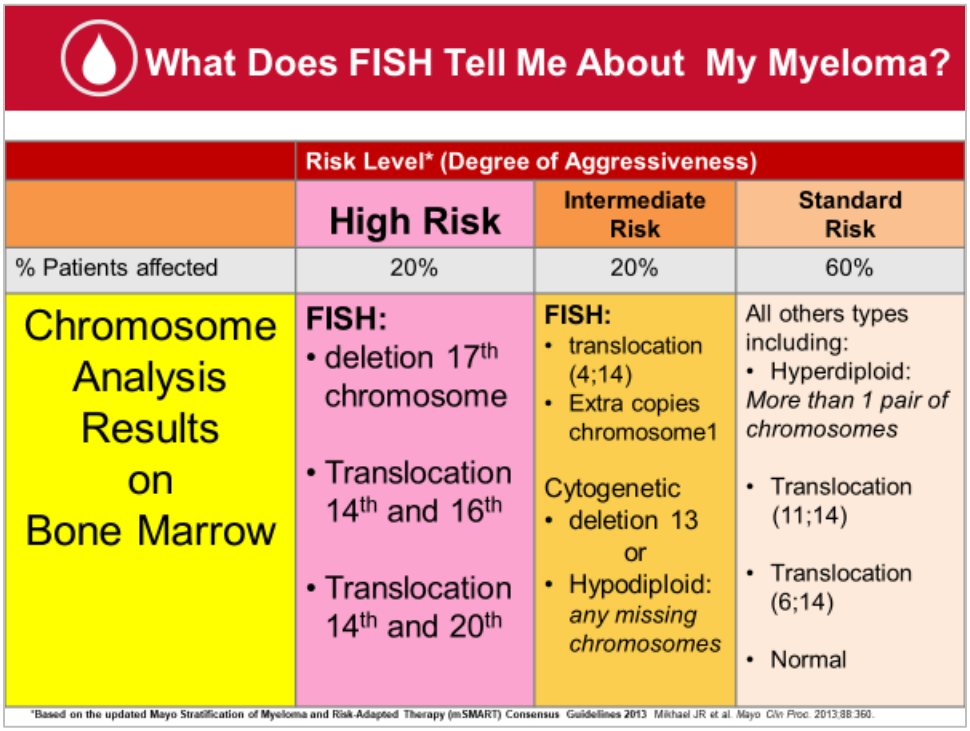


And how is that done? Well, inside all your cells, and here is a plasma cell, you have two sets of chromosomes; and the two sets of chromosomes in this little cartoon are either green or red. And you have one chromosome from mom, the green one, the one chromosome from dad, the red one, and then another chromosome from mom and another chromosome from dad. So we have two sets of chromosomes each from mom and dad. And this is a normal plasma cell.

Now if inside the plasma cells there's a mutation that happens, like in the next one, you see that there's a red chromosome, a green chromosome; and then there are two chromosomes stuck together, and that shouldn't happen. That's bad. That's a mutation that happens. That isn't in every cell in your body, of course, because then you'd have like three arms or six heads or something. But if it occurs just in the plasma cells, then those plasma cells grow out of control and become myeloma.

Here's another one where there's a green chromosome for chromosome 14, a red chromosome for chromosome #4, and then you see them stuck together, and that's the translocation, the stuck together of chromosome 4 and 14. And here's another one where the 14 is green, the 16 is red, and then you have a red and a green stuck together, which is 4 and 14 stuck together; and that's the mutation that causes myeloma.

One very frequent mutation that causes myeloma are triplet chromosomes that, and here's a patient that their plasma cells have three chromosome #7s. You should only have two, one from mom, one from dad. And having an extra chromosome is the mutation that causes the myeloma, among other mutations.



What Does FISH Tell Me About My Myeloma?

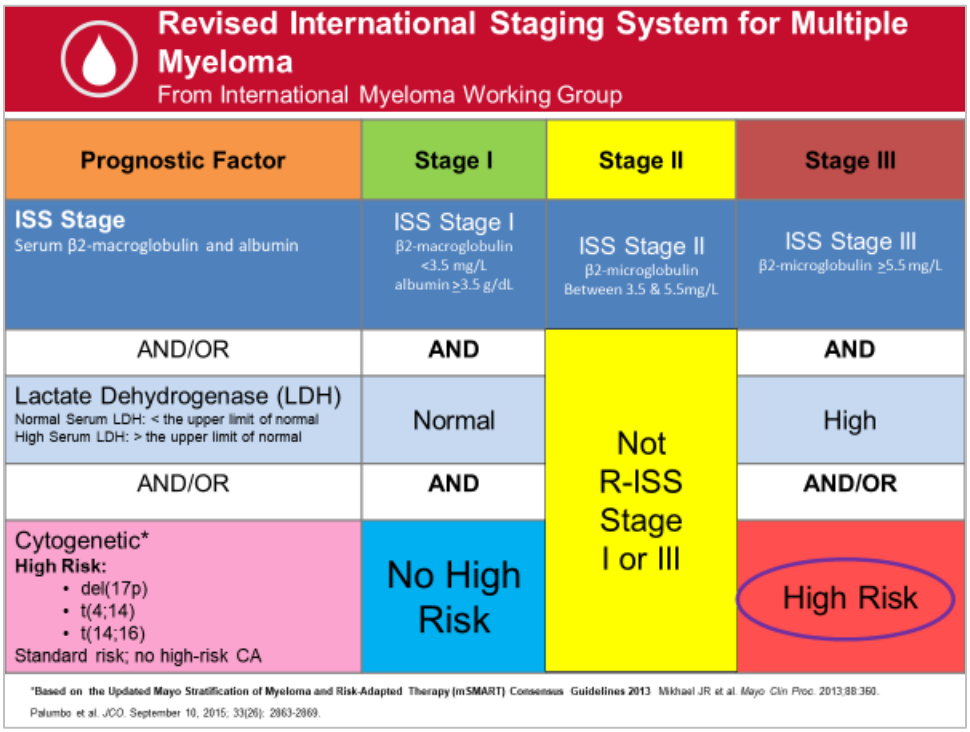
	Risk Level* (Degree of Aggressiveness)		
	High Risk	**Intermediate Risk**	**Standard Risk**
% Patients affected	20%	20%	60%
Chromosome Analysis Results on Bone Marrow	**FISH:** • deletion 17th chromosome • Translocation 14th and 16th • Translocation 14th and 20th	**FISH:** • translocation (4;14) • Extra copies chromosome1 Cytogenetic • deletion 13 or • Hypodiploid: *any missing chromosomes*	All others types including: • Hyperdiploid: *More than 1 pair of chromosomes* • Translocation (11;14) • Translocation (6;14) • Normal

*Based on the updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines 2013 Mikhael JR et al. Mayo Clin Proc. 2013;88:360.

And so it is really important to have that FISH data because it helps us determine the risk level or the degree of aggressiveness, how difficult it will be to treat the disease. Most patients will have standard-risk myeloma, and that is primarily having three sets of chromosomes or maybe four sets of chromosomes inside one plasma cell. Sometimes that's the translocation of chromosome 11 and 14 as a standard risk, and those are the easier patients where the disease is easier to control.

Intermediate-risk myeloma, you can have an extra copy of chromosome 4 or translocation of chromosome 4 and 14. And those you have to be a little bit more cautious of in treating those patients because the disease is a bit more aggressive.

And then there's the high-risk disease. Those are, again, the minority of myeloma patients, but those are defined by having a deletion of one of the 17th chromosomes or a translocation of 14 and 16 or a translocation of 14 and 20. And that helps us tell what the degree of aggressiveness and how we would approach an individual's multiple myeloma.



Revised International Staging System for Multiple Myeloma
From International Myeloma Working Group

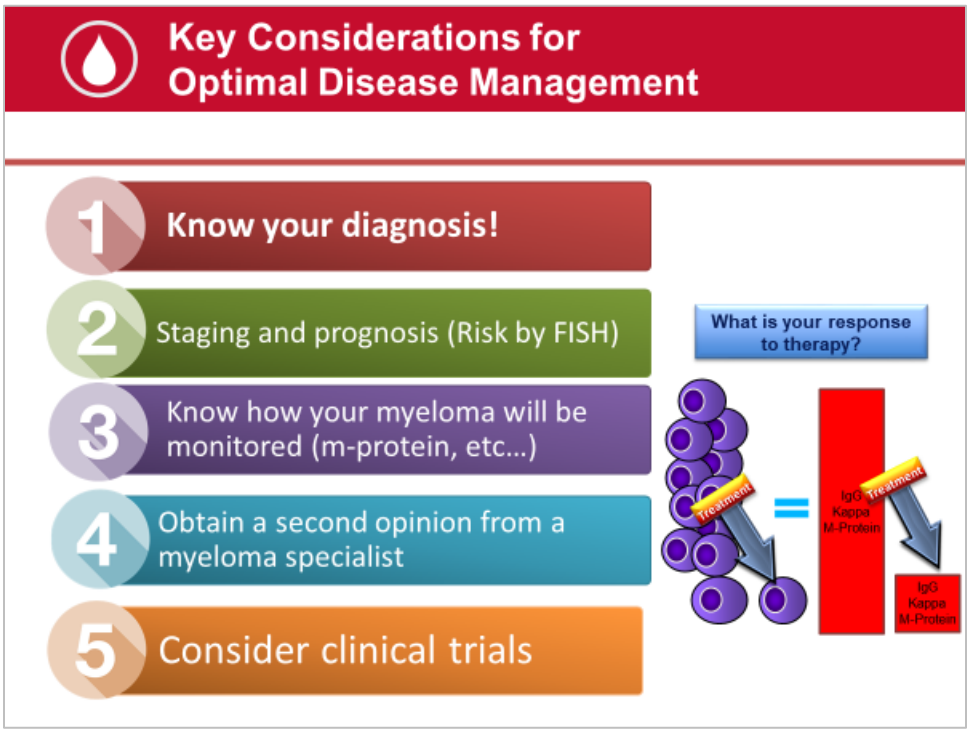
Prognostic Factor	Stage I	Stage II	Stage III
ISS Stage Serum β2-macroglobulin and albumin	ISS Stage I β2-macroglobulin <3.5 mg/L albumin ≥3.5 g/dL	ISS Stage II β2-microglobulin Between 3.5 & 5.5mg/L	ISS Stage III β2-microglobulin ≥5.5 mg/L
AND/OR	**AND**	Not R-ISS Stage I or III	**AND**
Lactate Dehydrogenase (LDH) Normal Serum LDH: < the upper limit of normal High Serum LDH: > the upper limit of normal	Normal		High
AND/OR	**AND**		**AND/OR**
Cytogenetic* **High Risk:** • del(17p) • t(4;14) • t(14;16) Standard risk; no high-risk CA	No High Risk		High Risk

*Based on the Updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines 2013 Mikhael JR et al. *Mayo Clin Proc.* 2013;88:360.
Palumbo et al. *JCO.* September 10, 2015; 33(26): 2863-2869.

And now we put all that together in the new staging system, and it is really important to know your stage of myeloma. We used to kind of ignore it when it wasn't working well, but now we have a very solid staging system for myeloma.

Stage I is when the beta-2 microglobulin is low, so not a lot of plasma cells, kidneys work okay, the lactate dehydrogenase, we talked about that earlier, that's a chemical that's released by the plasma cells, especially when the cells are dividing quickly. And when cancer cells are dividing quickly, the LDH will be high. And then you look at those cytogenetics that we talked about, that the high-risk cytogenetics will define Stage III.

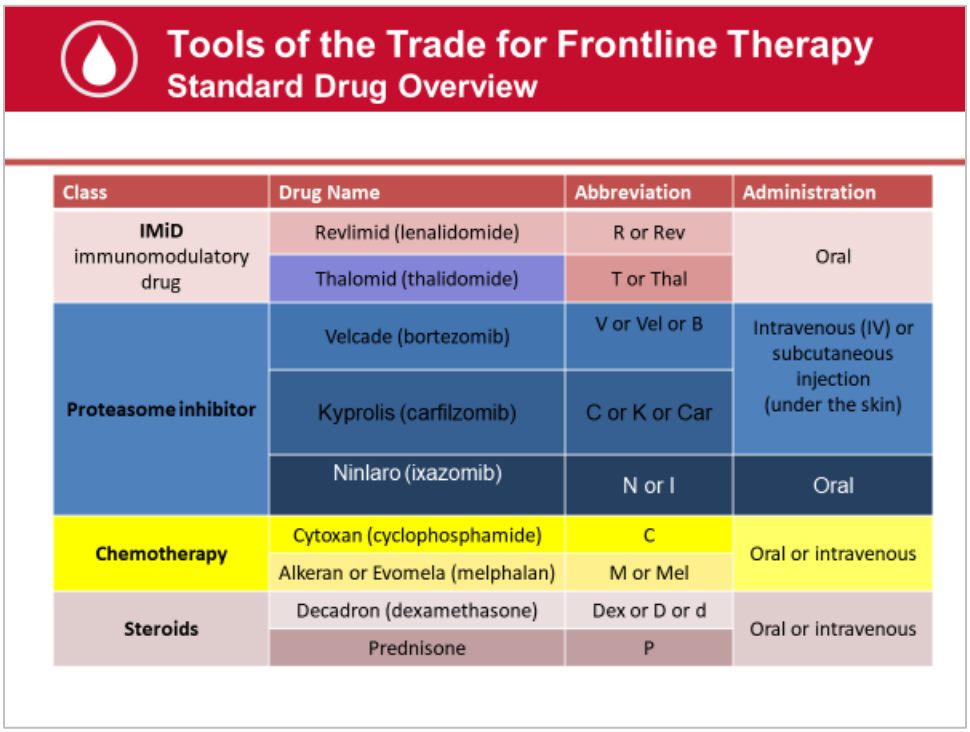
In Stage III, you have a high beta-2 microglobulin, lots of plasma cells. The LDH is high, they divide very quickly and they have the high risk cytogenetics on FISH. And there was a study that was done that patients who know their stage are more likely to participate in their decision-making with their doctor because you're, again, speaking the same language. And so it's important to know your stage.



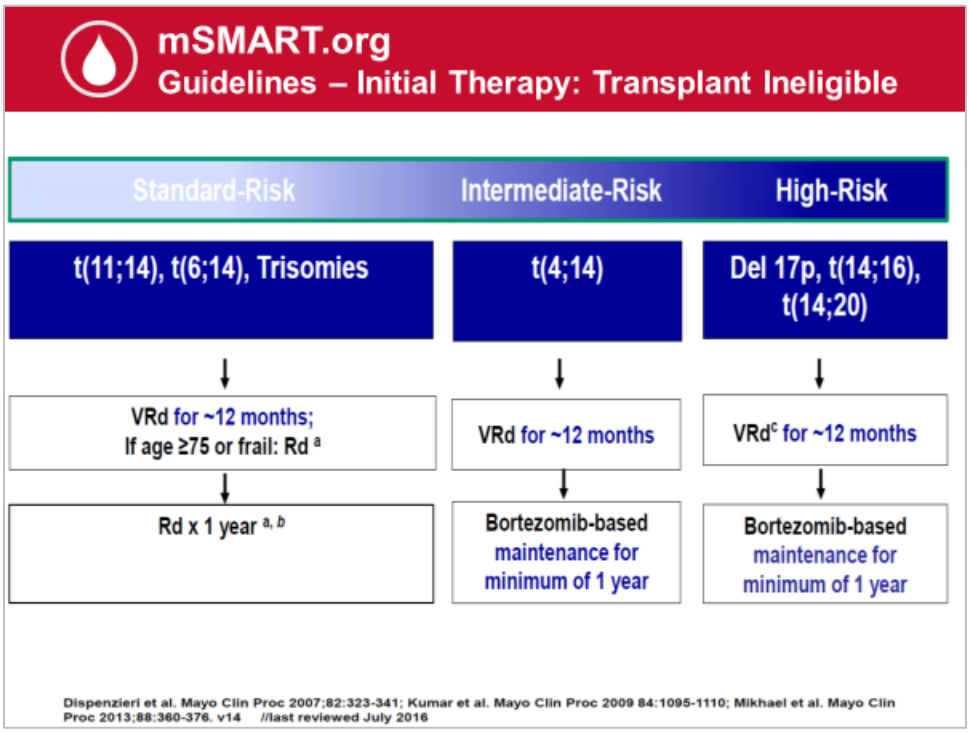
So, know your diagnosis. These are optimal disease-management tools. Know your diagnosis. Have it written down, and carry it with you when you go to second opinions or see your family doctor. Know your diagnosis. Know your stage and prognosis by FISH, and it usually is just a few numbers; but it tells you if you're high risk, standard risk, or intermediate risk because that will have an impact in decision-making down the line.

Know how your myeloma is monitored. Again, know your M protein. You need to know when to celebrate. You need to know that when the treatment brings down the protein levels, that means that the number of cancer cells have gone down. And if it goes back up, the protein goes up, then the myeloma is beginning to return; so, it's important to know your myeloma protein level.

Always obtain a second opinion from a myeloma specialist. As a myeloma specialist myself, I send my patients for second opinions; and it's really important to especially look for clinical trials that may be available to you. And then, finally, again, consider clinical trials because myeloma is one of the fastest moving cancers in research; and there are multiple clinical trials available.

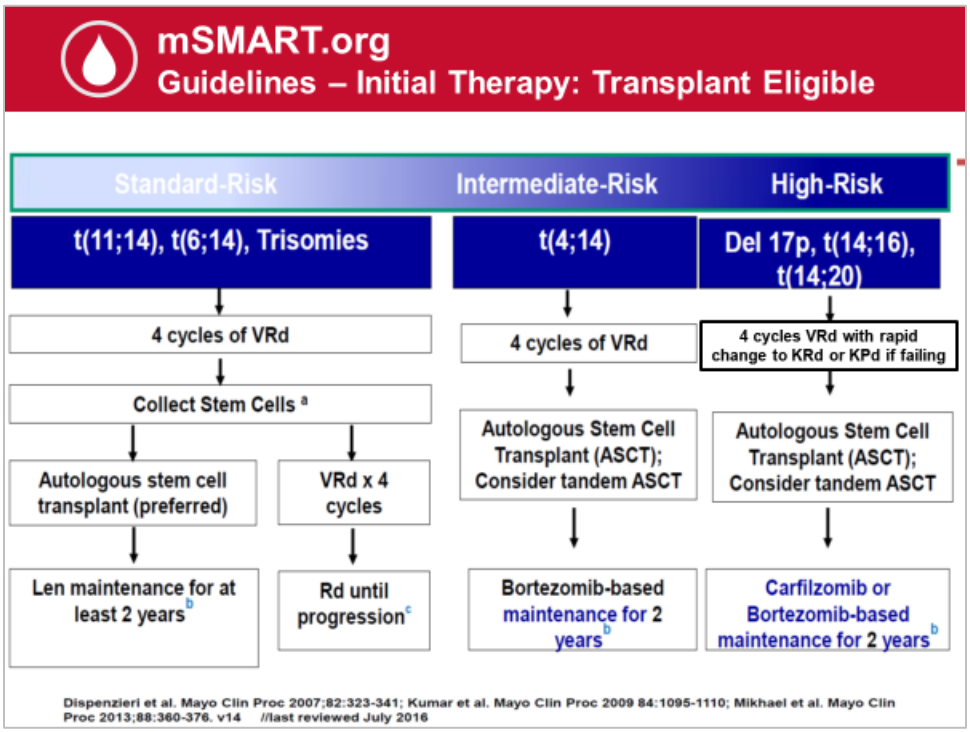


So how do you treat multiple myeloma these days? Well, it's important to know the tools of the trade. There are the immunomodulatory drugs. Revlimid® (lenalidomide) and thalidomide are common drugs that we use. They're both pills. They're the proteasome inhibitors, and the proteasome inhibitors are Velcade® (bortezomib), Kyprolis™ (carfilzomib) and Ninlaro® (ixazomib). Velcade is a shot under the skin or an IV. Kyprolis is an IV, and Ninlaro is a new drug which is an oral version of Velcade. We do still sometimes use chemotherapy, Cytoxan (cyclophosphamide) and we use melphalan for transplant. And then, unfortunately, we still are stuck using steroids in combination with the other tools of the trade, either prednisone or Decadron.



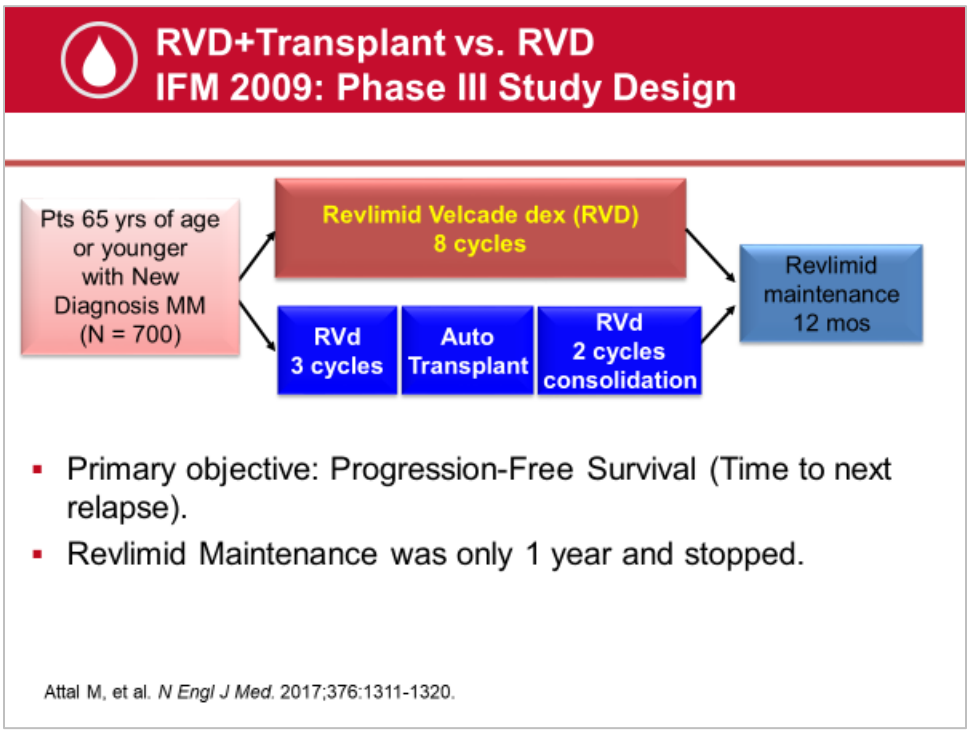
And one source that you can always look at and bring your doctor to is the mSMART.org guidelines. These guidelines are for myeloma and amyloidosis at all stages, and it is really a consensus statement about how we treat myeloma from the Mayo Clinic.

For standard risk, and if you look, for all the risks of disease, standard, intermediate, and high risk, and patients who were ineligible for transplant, we usually use Velcade-Revlimid-dexamethasone for a year; and then we always use some type of maintenance therapy. And you see the importance of knowing your risk because if you're intermediate or high risk, we usually use Velcade or bortezomib for high-risk disease and Revlimid and/or dex for standard-risk disease. So again, stage and risk are important.



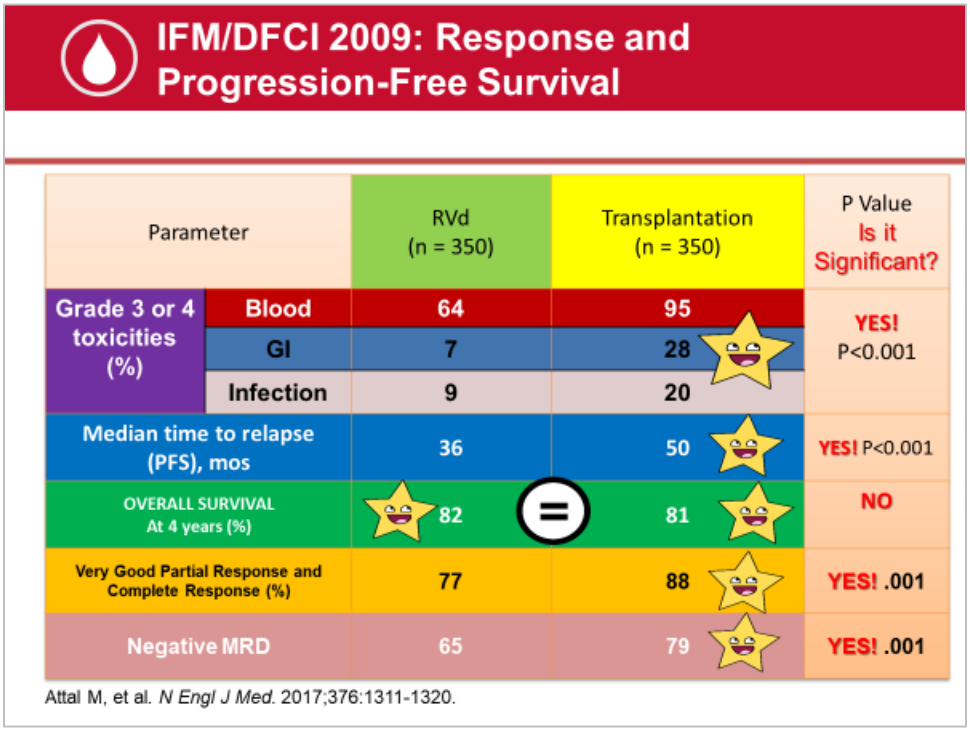
For transplant eligible newly diagnosed patients, again, we usually use Revlimid-Velcade-dexamethasone for the standard and intermediate risk; and we may need, high-risk patients sometimes can lose their response; and therefore, we have to be ready to change rapidly to different drugs, regimens. And so, sometimes you'll start out with a Revlimid-Velcade-dexamethasone and then change to Kyprolis-Rev-dex or Kyprolis-pomalidomide-dex if they're failing. All followed by stem cell transplant and then maintenance therapy,

so those are kind of the standard treatments that we use for induction therapy for myeloma.



And let's talk a little bit about transplant. So, there's the study that we usually point towards these days. It's a study done in Europe for newly diagnosed myeloma, and this trial we got patients who were 65 years of age with new myeloma, and they were randomized to either chemotherapy only,

Revlimid-Velcade-dexamethasone (RVD) for eight cycles, and then they went on maintenance or they got a transplant. Or they got the RVD for three cycles, transplant, consolidation RVD and then maintenance. And the point of the trial is to see does transplant at the beginning of therapy equal or is better than going straight through RVD and then doing a transplant later on. But all patients in this European trial went on Revlimid maintenance for 12 months.



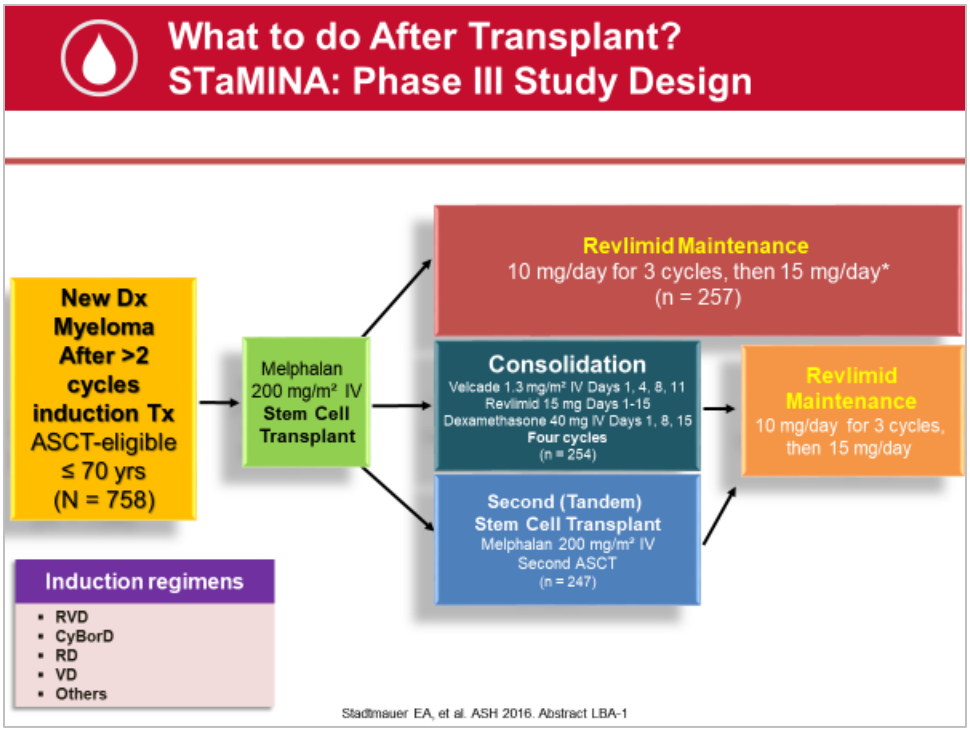
So how did that trial turn out? Well, if you look at RVD where the patients received eight cycles of RVD versus RVD and transplant in yellow, that the winner for toxicities and side effects was, of course, transplant because you get a lot of chemotherapy at once; and that does cause low blood counts, some nausea, and infections. So, but for toxicities, transplant wins, although those toxicities are very limited; and people recover very well.

When it comes to how long until a relapse, transplant wins. Progression-free survival, transplant wins by quite a bit. That patients remain in their response longer with transplant than with treatment only.

Now the survival is equal, so the overall survival at four years was very good. Both, 80% of people were alive at four years, which isn't bad for a group that's 65 years of age.

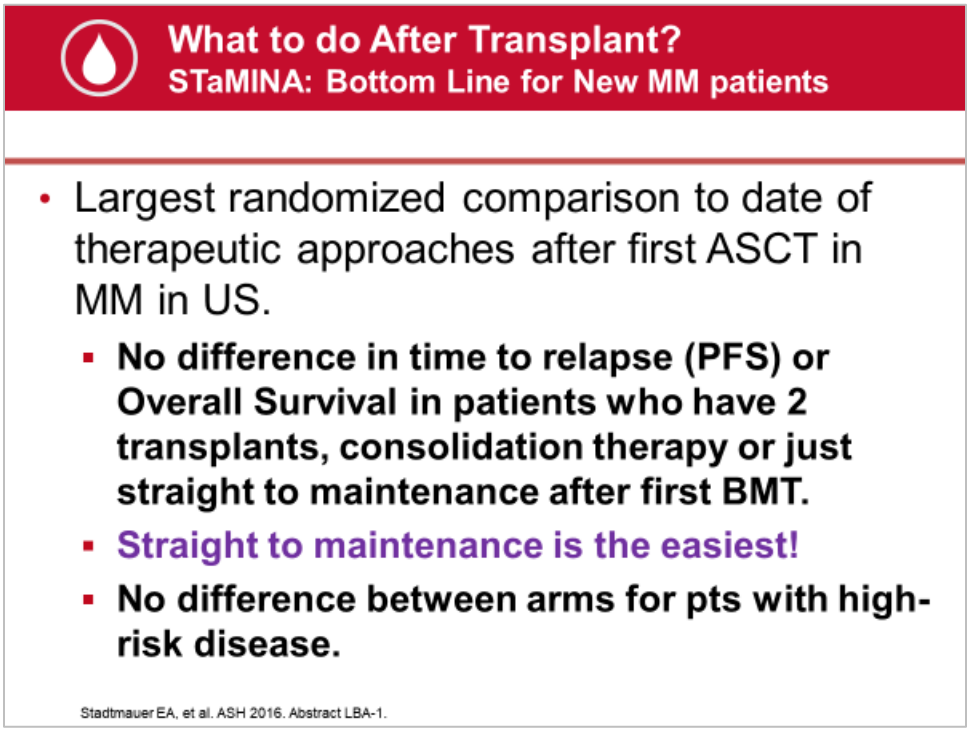
And the one trick about this is that a lot of the patients in this European trial who received RVD got a transplant later on for their relapse. And so, although the RVD patients without transplant had a relapse earlier, they were salvaged with transplant; and it didn't really matter if they had transplant up front or if you waited until the first relapse. So, there was no difference in overall survival; both are winners there.

For depth of response, transplant won; and for minimum disease negativity, again, transplant won. So, we usually recommend transplant for transplant-eligible patients. In the United States, it's not so much chronologic age, but it's more physical age that is the discriminator for transplant.

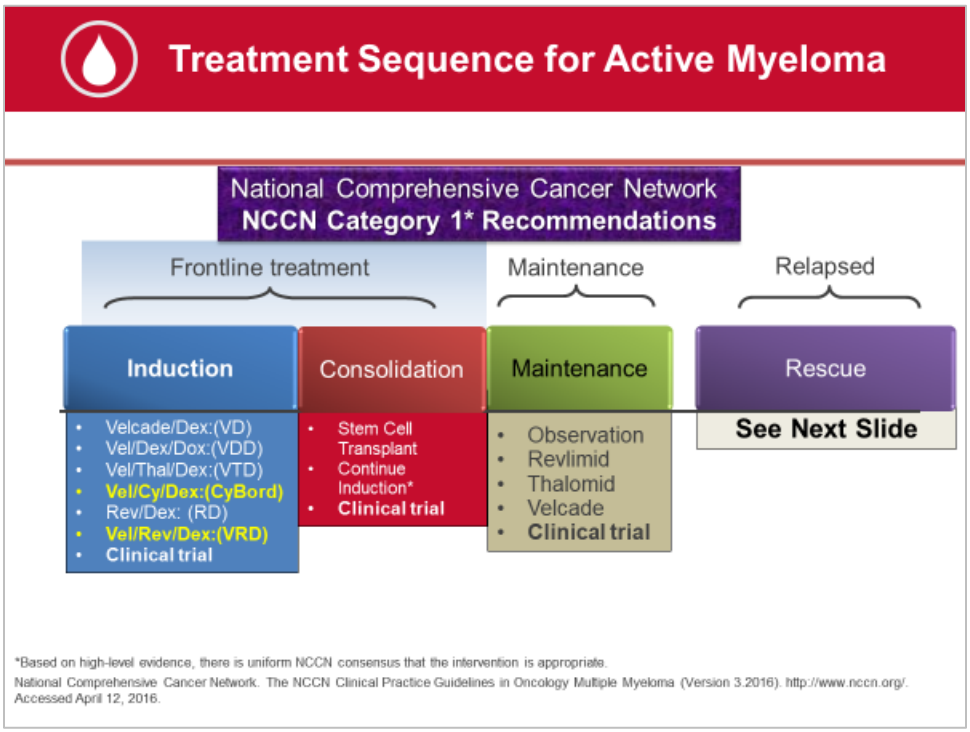


And then what to do after transplant. Just a couple years ago, just a year ago, one of the largest trials in the United States asked the question of do you need more therapy after transplant? And in this trial, it got patients that underwent stem cell transplant. They either went straight to Revlimid maintenance, consolidation with RVD, and then Revlimid maintenance or a second transplant.

And this trial was really important because a lot of people were getting consolidation after undergoing stem cell transplant.

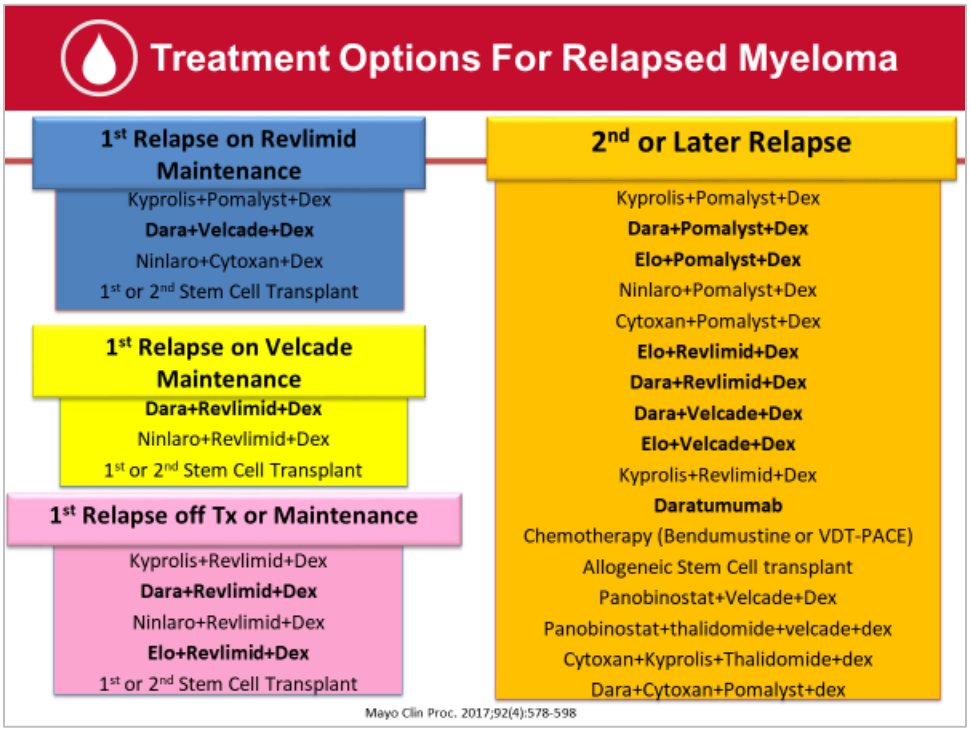


And what this trial showed is that there was no difference in time to relapse for patients after receiving a transplant. Overall survival and time to relapse, all the same. So, it just made sense just to go straight to maintenance therapy, and that's what we now do based on the STaMINA trial. And with high-risk patients, it didn't matter, that going straight to maintenance after transplant was the way to go.



So, the current National Comprehensive Cancer Network (NCCN) guidelines for upfront treatment, there are a variety of choices; but we usually use either Cytoxan-Velcade-dex or Revlimid-Velcade-dex or clinical trial. That's followed by a consolidation of some type, usually stem cell transplant or continued induction. And then everyone goes on, most patients go on maintenance because maintenance therapy has been shown to increase the time to next relapse and overall survival, especially for Revlimid.

And so, we don't do much observation anymore after induction therapy.

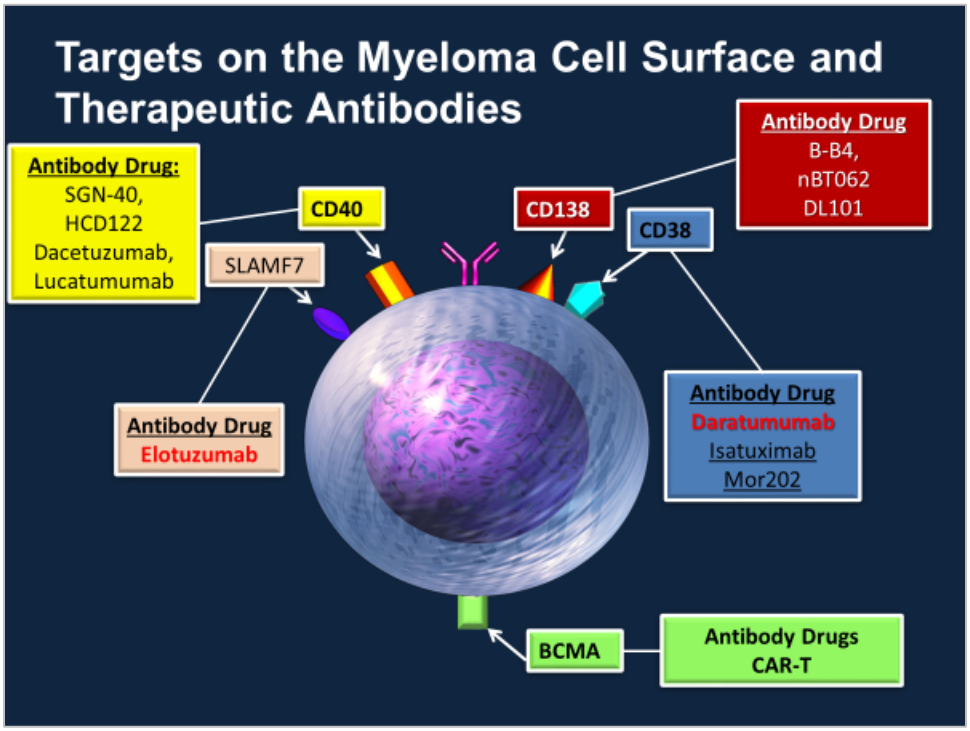


And when the myeloma comes back, there are a number, a multitude of different therapies to choose from. Some have been approved by the FDA (Food and Drug Administration), some are currently in clinical trials, but there are a multitude of different therapies for relapsed myeloma, which then gives the opportunity to ask what your goals of therapy are and what fits best into your life.

And it is really important to ask your doctor if your myeloma comes back for clinical trials because the reason that we have so many choices in myeloma therapy at relapse is because patients participate in clinical trials.

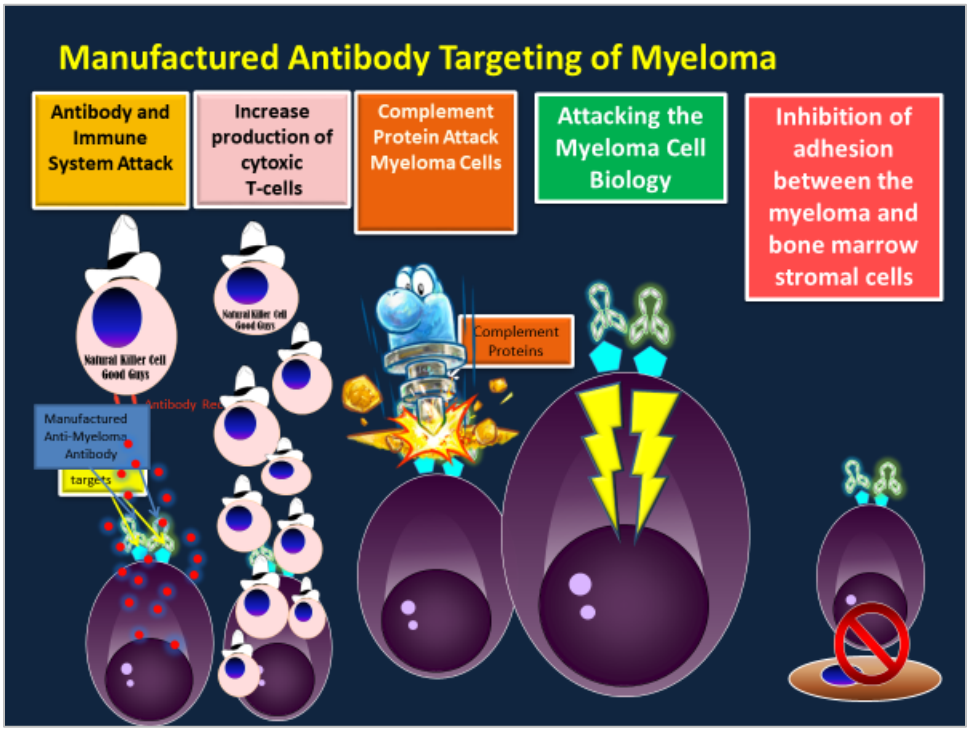
So, it really comes down to what's best for you. What is a therapy that you want? And so, make sure you talk to your doctor about your age, clinical trials, other medical problems and really what you prefer. And it's important to speak up about it.

So, we'll talk now about advances in myeloma research…



…and one of the biggest advances have been the immune therapies. And on top of the plasma cell, we found that there are proteins on top of the plasma cell that identify them as plasma cells. Your body has to be able to tell what's an eyeball cell and what's a plasma cell, and the plasma cells are defined by having SLAM7 (signaling lymphocyte activation molecular family 7), CD38 (cluster of differentiation 38) and CD138. Because your body won't make antibodies against plasma cells, we've made them in the laboratory so that it, and they are antibodies against the proteins on top of plasma cells. And so, it fools your body into thinking that the plasma cells are an infection to get rid of, and that's why these drugs work.

The ones in red, elotuzumab is against SLAM7; and daratumumab is against CD-38; and there are a number of other drugs in production looking at other surface antigens. And, of course, there's BCMA (B-cell mutation antigen), which is the surface protein on plasma cells that are used for CAR T (chimeric antigen receptor T-cell) therapy that we'll talk about in a second.

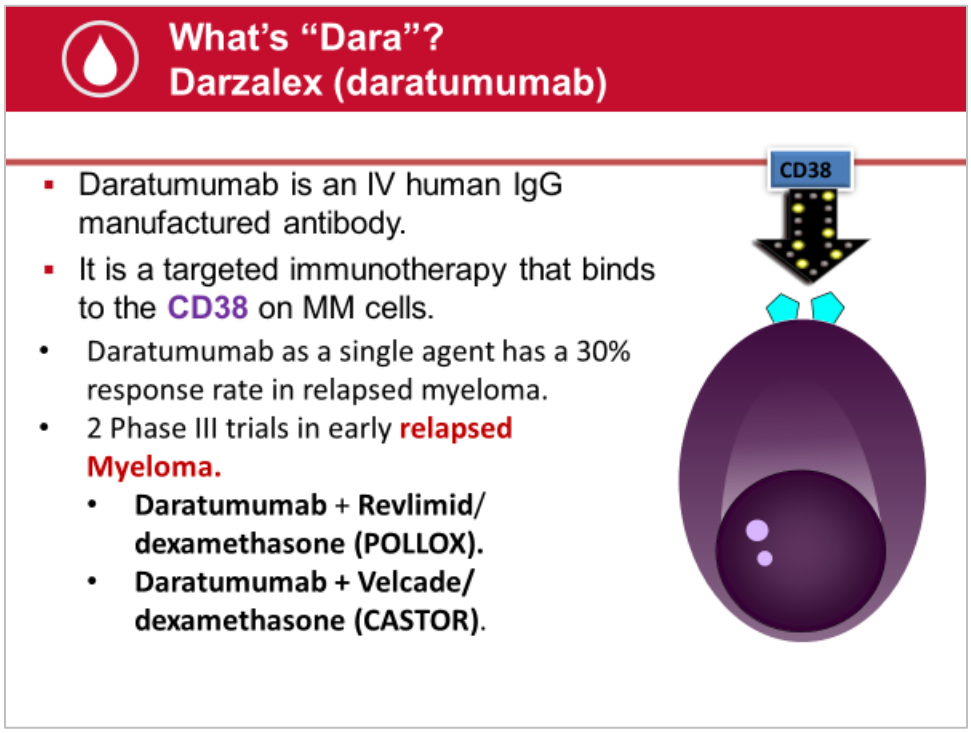


So how do these antibodies work? Well, they're the myeloma surface antigens in bright blue. And then we infuse the manufactured antibodies; and as soon as an antibody touches anything, then the immune cells come in and descend upon them to get rid of them as if it got rid of an infection. So, they'll produce granules that will destroy the plasma cells as if it were an infection. Also, when the antibody sticks to the plasma cell, the elotuzumab or daratumumab right now, that those immune cells will engage in hand-to-hand combat with those plasma cells to destroy them.

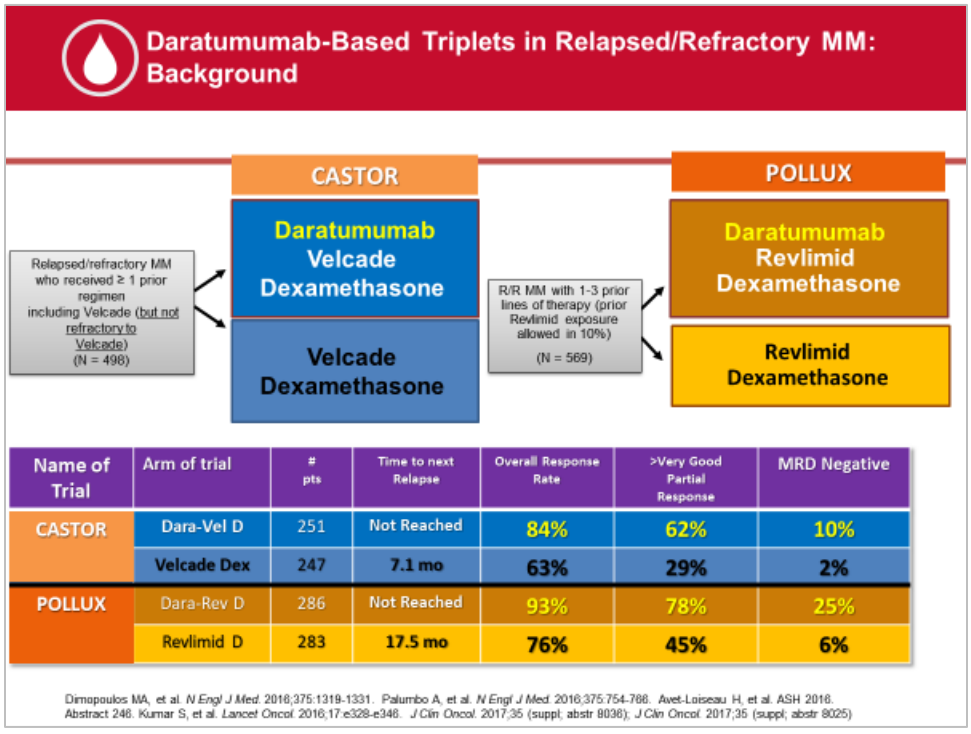
Also, when the antibody sticks to the plasma cells, it activates an ancient part of our immune system called complement which complements our normal immune system and bores holes inside the plasma cells so they leak and bleed to death as well as being attacked by the immune cytotoxic T-cells and the granules of the cytotoxic T-cells.

On top of that, the antibodies actually cross-link the receptors inside the plasma cell which cause them to short circuit and die spontaneously. So even without the immune system working, the antibodies work to destroy plasma cells.

And then, finally, because we talked about how plasma cells are dependent upon the bone marrow microenvironment, that if an antibody sticks to plasma cell, the bone marrow assumes that it's a bacteria and will kick out the plasma cell. And if the plasma cells aren't sticking to the bone marrow, then they can't live, and they die; and so, there is a five-pronged attack that the antibodies use to destroy myeloma cells.



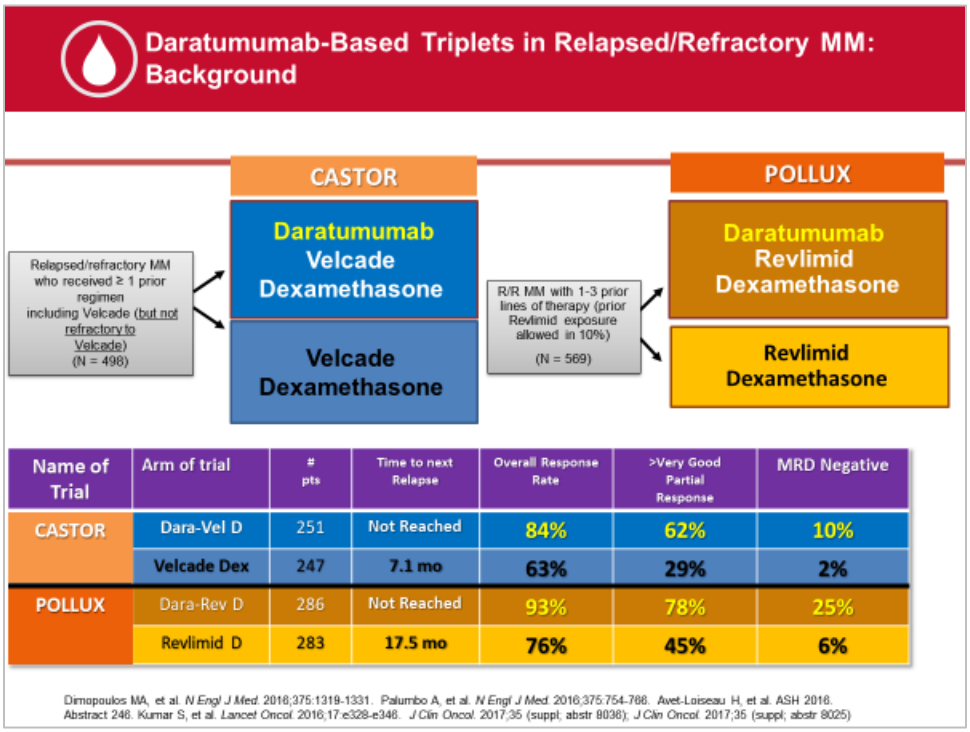
Darzalex™ was one of the first antibodies approved, and they, as a single agent, had a 30% response rate; but it really began to shine when combined with other drugs.



And that was in the CASTOR trial and POLLOX trial where patients were given Velcade and dexamethasone for the CASTOR, Revlimid and dexamethasone for the POLLOX, and then half the

patients had daratumumab added on to their Velcade-dex or Revlimid-dex space. If you look at the results, it is phenomenal. On the POLLOX arm, if you look at the overall response rate, the Rev-dex alone, 76% response rate, not bad. You add this infusion antibody on, 93% response rate, a huge jump.

If you look at minimal residual disease negativity, that adding on daratumumab, both arms, it jumps up significantly. And the time to next relapse hasn't been reached. Those patients are still doing well on the drug combination while the patients on Velcade-dex and Revlimid-dex have already relapsed. So, this was a game-changer in myeloma that you can add on this antibody, and it has incredible results.



Name of Trial	Arm of trial	# pts	Time to next Relapse	Overall Response Rate	>Very Good Partial Response	MRD Negative
CASTOR	Dara-Vel D	251	Not Reached	84%	62%	10%
	Velcade Dex	247	7.1 mo	63%	29%	2%
POLLUX	Dara-Rev D	286	Not Reached	93%	78%	25%
	Revlimid D	283	17.5 mo	76%	45%	6%

Dimopoulos MA, et al. *N Engl J Med.* 2016;375:1319-1331. Palumbo A, et al. *N Engl J Med.* 2016;375:754-766. Avet-Loiseau H, et al. ASH 2016. Abstract 248. Kumar S, et al. *Lancet Oncol.* 2016;17:e328-e346. *J Clin Oncol.* 2017;35 (suppl; abstr 8036); *J Clin Oncol.* 2017;35 (suppl; abstr 8025)

So now we have trials going on with daratumumab-Pomalyst-dex, which is actually approved by the FDA in heavily treated myeloma, 60% response rate. And there was a trial done with daratumumab-Kyprolis-Revlimid-dex for newly diagnosed myeloma, 100% response rate, and 86% very good partial responses. So deep responses, 100% response rate for newly diagnosed myeloma. And, of course, this is in a clinical trial and it did have side effects; but this is remarkable to see the combination of treatment and the immune system.

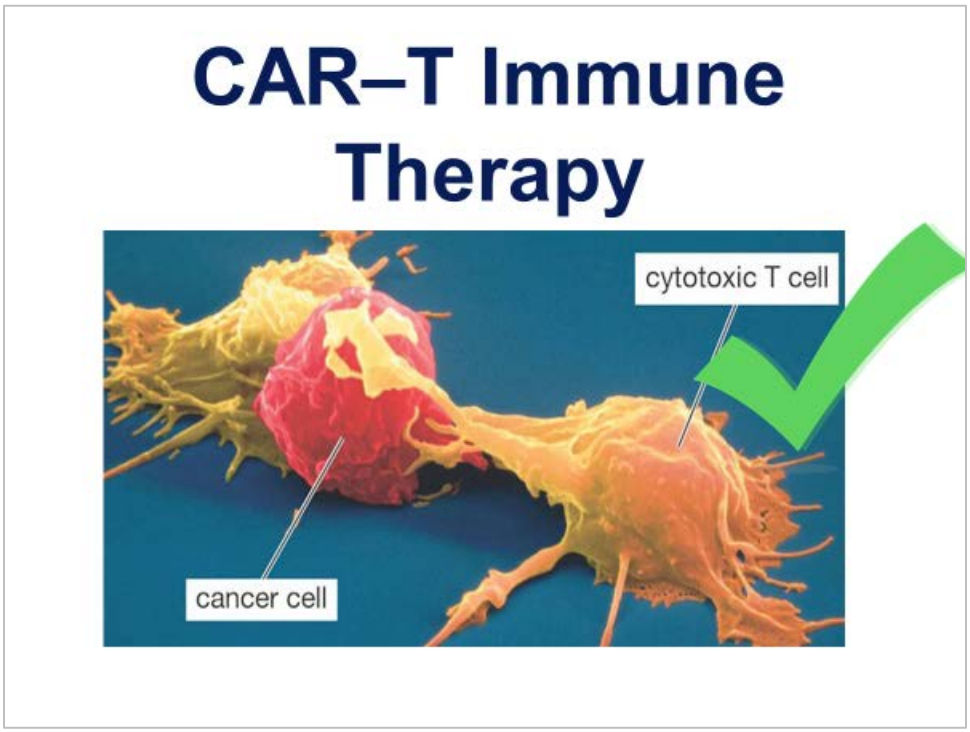
Performance of Empliciti =(Elotuzumab)= "Elo"

Regimen	Phase	Patient Population	Number of patients	Outcomes	Adverse Events
Elotuzumab + Revlimid+ Dexamethasone Vs. Rev Dex ELOQUENT-2	3	**646** ERD:321 RD:325	RRMM 1 to 3 prior regimens	**EloRD vs. RD** **Response rate: EloRD: 79% vs RD: 66%** Median Duration of response: Elo RD:19.4 vs RD:14.9 months	**Severe toxicities:** Low lymphocytes, fatigue, pneumonia •• **Infusion reaction** in 10% of patients
Elotuzumab + Velcade + Dexamethasone Vs. Vel Dex (Palumbo et al, 2015)	2	**152** Ebd:77 Bd: 75	RRMM 1 to 3 prior regimens	**EloVD vs. VD** **Response rate: Elo VD: 65% vs VD: 63%** Median Duration of response: **EloVD:9.9 vs VD:6.8 months**	**Severe toxicities:** Low platelets (9%), infections (23%) •• **Infusion reaction** in 5% of patients
Elotuzumab + Pomalyst + Dexamethasone (Jagannath et al, 2017)	2	53	RRMM 1 to 3 prior regimens	****Very Early Data after 3 cycles** 77% patients remain on treatment** **9%** discontinuation for disease progression	**Most common: fatigue, infections, cough, anemia** **Severe Toxicities:** Infections (13%), Pneumonia (9%)
Elotuzumab + Lenalidomide+ Bortezomib+ Dexamethasone (Laubach J, et al. ASCO 2017)	2	40	**Newly diagnosed, MM**	Response rate after 4 cycles: **Overall: 97%** >VGPR: 88% Median Duration of Response: **Not Reached**	**Most common adverse effects: Infection (50%) fatigue, peripheral neuropathy, edema, leukopenia**

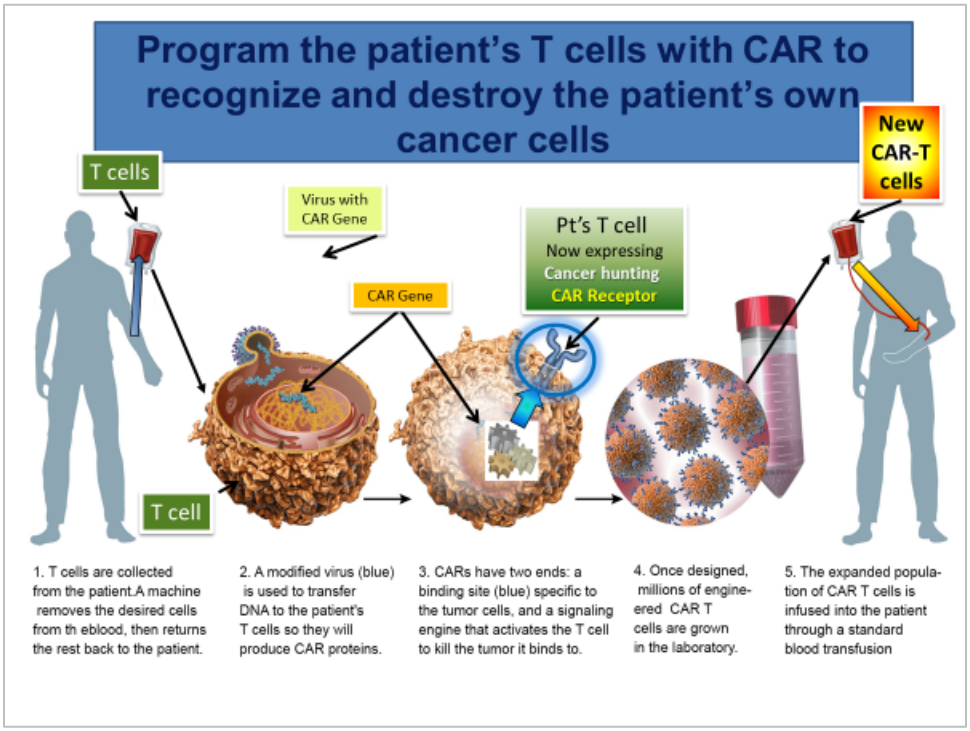
The elotuzumab, the other antibody approved by the FDA, or Empliciti™, again fantastic response rates for relapsed-myeloma, either combined with a Revlimid or with Velcade-dex, an 80% response rate, 65% response rate. When elotuzumab is combined with Pomalyst (pomalidomide) for relapsed myeloma, fantastic response rates; and we with Dana-Farber had finished a trial using elotuzumab and RVD therapy for newly diagnosed myeloma. Overall response rate, 97%, and most of those are very good responses. And still those patients are responding very well to their initial therapy. So, again, the combination in newly diagnosed and relapsed myeloma, by adding on the immune therapy, phenomenal results. I'm really excited about that.

So now we'll talk about CAR T therapy, and that was a Model T back there, that's CAR T.

This is my favorite slide of all time. Mr. T in a car, so CAR T. Mr. T. I think that's funny. I still laugh at that.

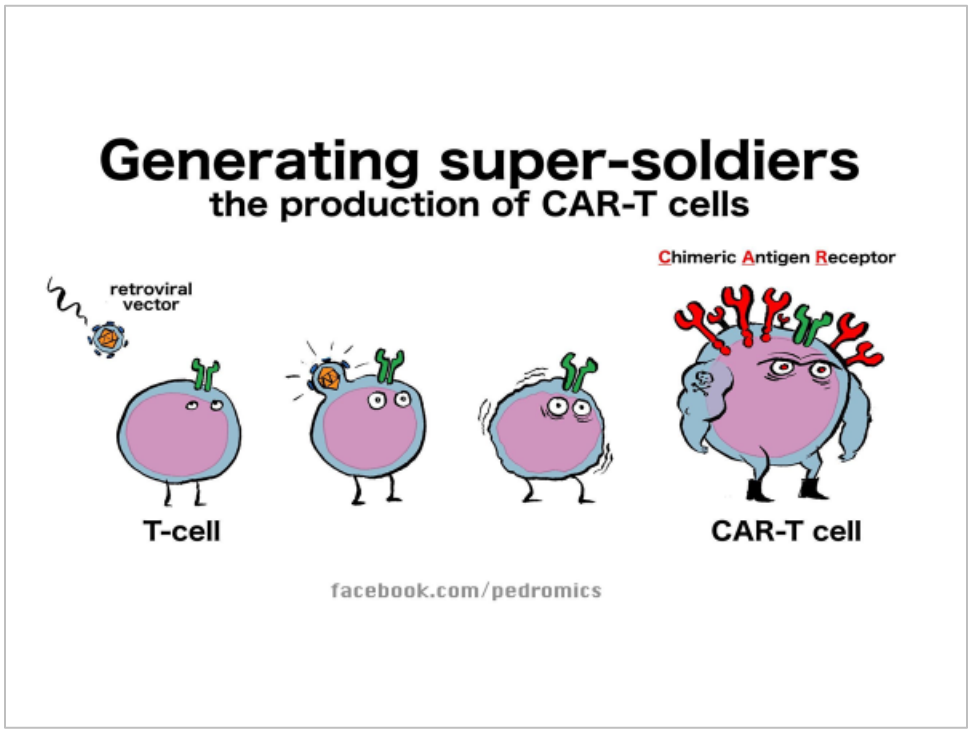


What we're really going to talk about is a CAR T, cytotoxic T-cells killing cancer cells. So how does that work?

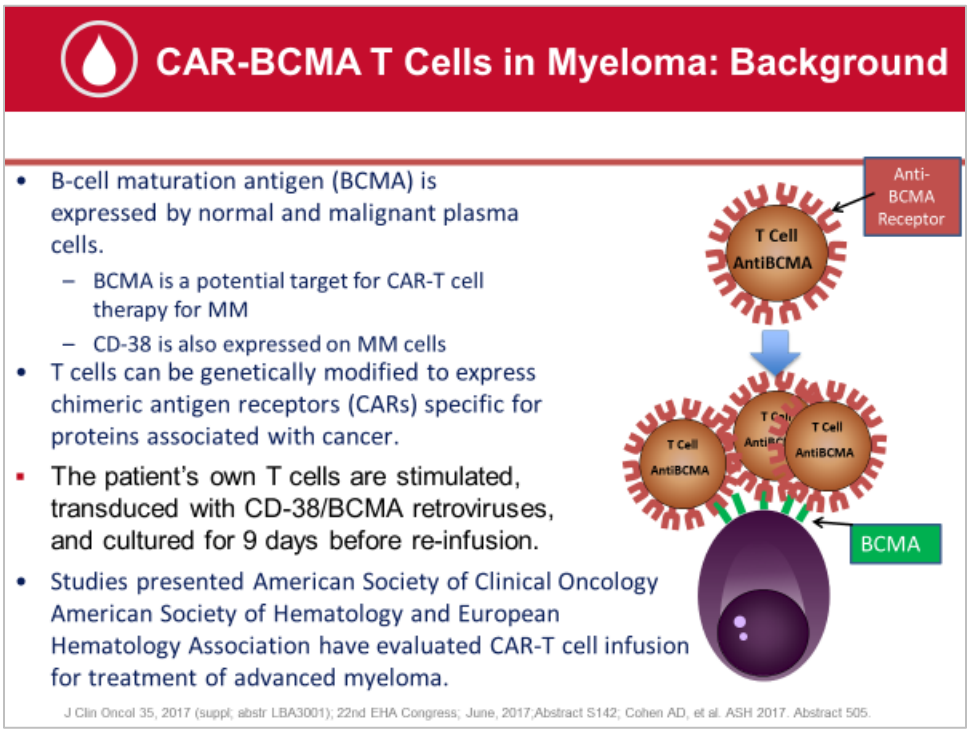


Well, T-cells are a type of white blood cell that kills cancer cells. They kill viruses and cancer cells; that's what T-cells do. And chimeric antigen receptors help T-cells find cancer cells to destroy. Now if your T-cells aren't hunting cancer, we can reprogram them to hunt cancer. So how do we do that?

Well, we obtain T-cells from the body the same way we obtain stem cells, through apheresis. We collect those T-cells and then we take them to the laboratory. And in the laboratory, we get a virus that has a human gene inside of it. And when we expose the virus to the T-cells, that virus will insert the gene, the cancer-fighting gene inside the patient's T-cells in the laboratory. So now the CAR gene is expressed inside the patient's T-cell, and then the body uses that new information to produce the chimeric antigen receptor, the cancer-hunting protein that helps the T-cell find the cancer that wasn't there before. So, a brand-new cancer-hunting protein. We then grow the T-cells in culture so there are a whole bunch of them; and then we infuse them back into the patient, and they immediately go hunting for myeloma, which is really exciting.

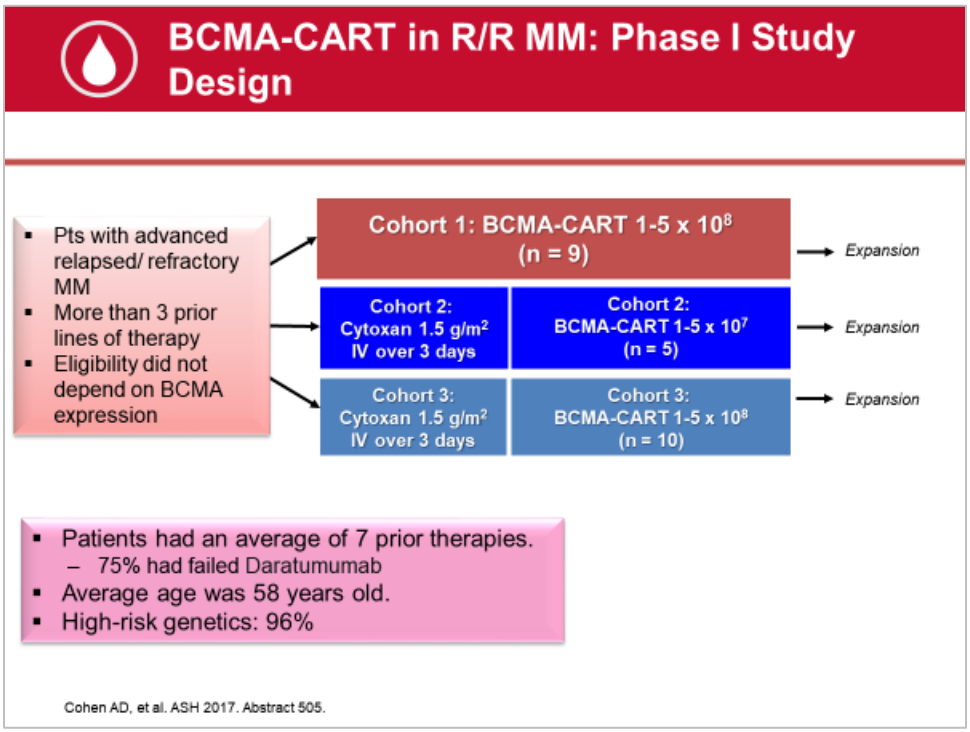


The easy way to think of it is that there's a T-cell. The virus infects the T-cell. The T-cell then shakes a little bit, and all of a sudden it becomes a cancer-hunting monster to go hunt down cancer cells specifically.

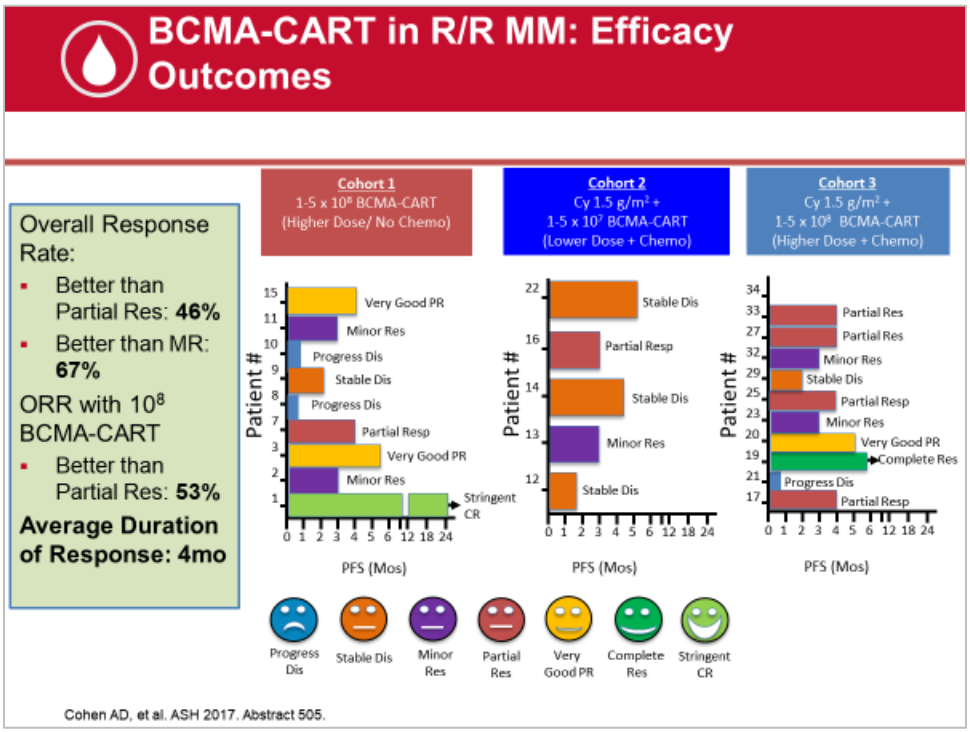


So, in myeloma, we use BCMA as the target for the T-cells. And the T-cells are modified to express BCMA receptors, and they are infused into the patient, grown in culture, and infused into the patient; and they go right for the myeloma cells and destroy them. And, hopefully, they grow and grow inside the patient so that it becomes a therapy in and of itself.

And there are several presentations over the past two years on CAR T-cells for myeloma,



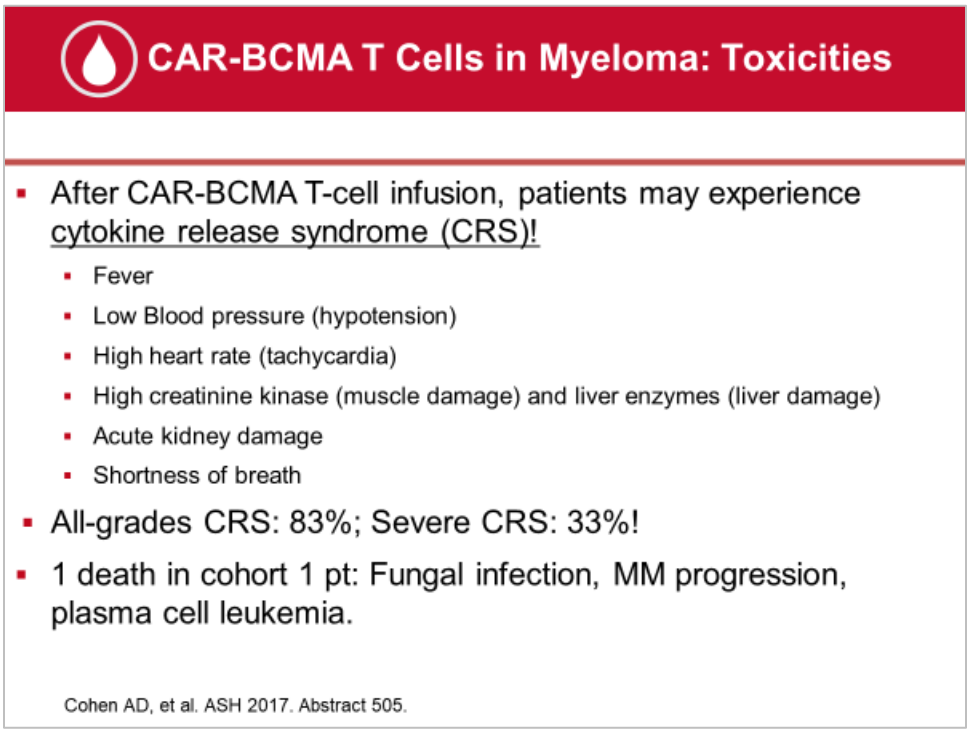
and this is one result that was presented at the last American Society of Hematology meeting where they broke, they had patients that had lots of prior therapies, had failed just about every therapy, most had high-risk cytogenetics; and they were younger people, and they either received CAR T-cells alone or CAR T-cells with chemotherapy.



The chemotherapy was there in order to make room for the CAR T-cells. So, there was no other part of the immune system working at that time.

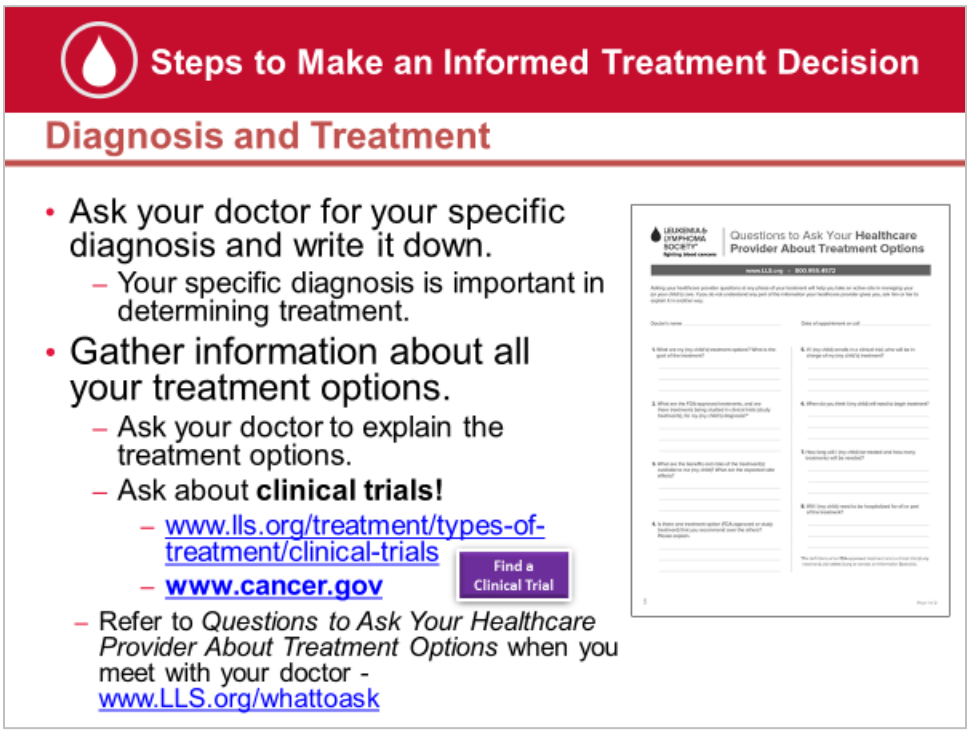
And how well did it work? Well, for these really heavily pretreated patients that had failed all other therapies, there were really good responses across the board. So, the stringent complete response, the smiley green guy, occurred in one patient and is still in a complete response months after receiving the CAR T-cells. For the first cohort, there are lots of very good partial responses, some stable diseases. And the stable disease is not bad for having such high-risk disease.

So, this was tested in a high-risk cohort with about a 70% response rate. The duration of response was short in this particular trial, but there are other CAR T-cell trials that have gone on that have very good results, on the order of response rates in order of 70 to 90% and have had longer lasting. So, there are lots of CAR T-cell clinical trials that are out there, and they're expanding, thank goodness.



The one side effect of CAR T-cell therapy is cytokine release syndrome, where patients have high fever, low blood pressure, high heart rate. They can have kidney damage, shortness of breath, and they can have neurologic changes. In this particular study, most patients had some type of cytokine release syndrome, but only 33% had severe cytokine release syndrome. There was one death, which for this high-risk population, was remarkable; and it was due to myeloma progression. But, again, it's the beginning of a whole new world of myeloma therapy for patients, and it's now being expanded significantly for patients, including randomized trials at many centers using CAR T-cells that'll be opening in the next few months. So, keep your eyes open for that.

So, we'll end with communication. Improving communication between the physician and patient.

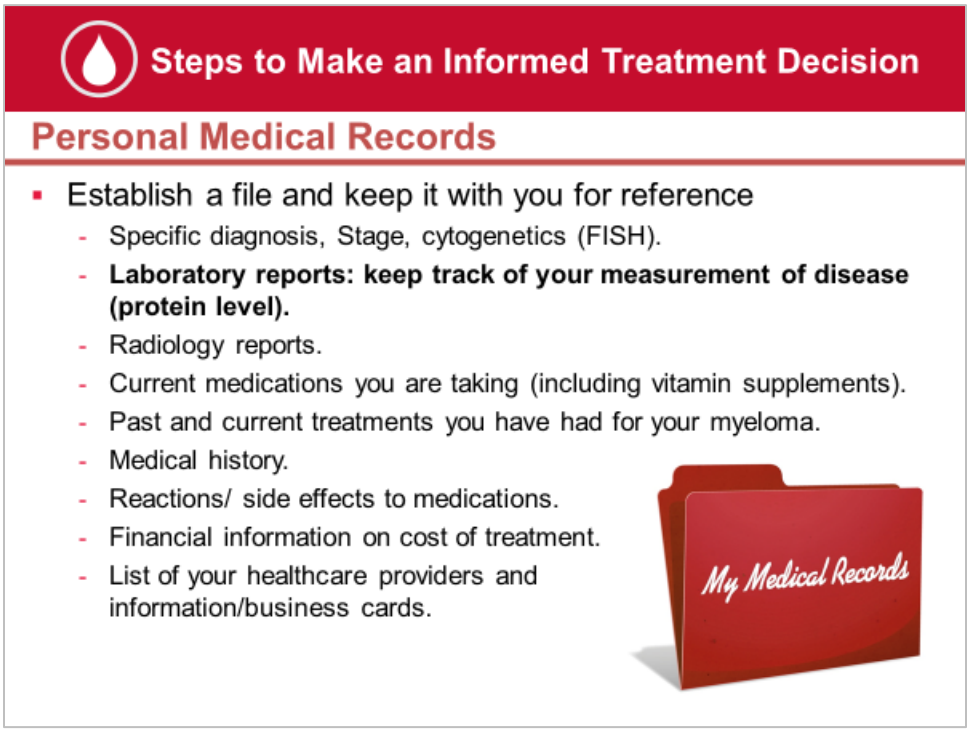


So, the way to make an informed decision is to make sure that you ask your doctor about your diagnosis and write it down and discuss your specific treatment regimen. Gather all the information that you can and ask your doctor questions. Ask your doctor questions, question your doctor about

the decisions. And one thing that can really help is the LLS has a website that helps you come up with clinical trials that are available to you.

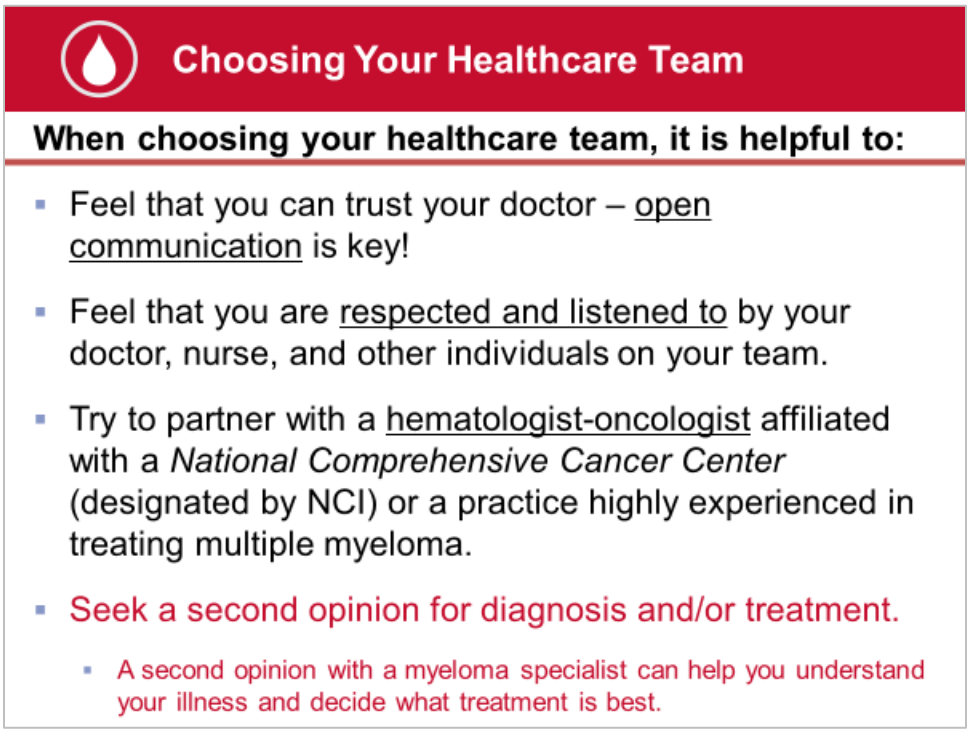
Also, cancer.gov, from the National Institutes of Health (NIH), if you go to cancer.gov, it has a purple box just like that, that will follow you all over the website. You press that, and it can lead you to myeloma clinical trials.

I love this part of LLS.org. The biggest question I get is what should I ask my doctor, what should I ask you when a patient comes to visit me with myeloma? And LLS can help with that. What to Ask is a fantastic tool, and it helps you write down and organize your thoughts before you see your physician, which is really critical in making sure that you have an informed decision about the therapy that you have.



Make sure you keep a file of your personal records—your diagnosis, your FISH, your lab reports. Make sure you get your lab results because, remember, how well you're doing is based on the protein level and the radiology reports. Make sure that you write down your reaction to the side effects to medications, your medical history and bring your financial information because myeloma therapy is expensive these days; and you need to be able to discuss the cost of treatment with your providers in the clinic that you work in.

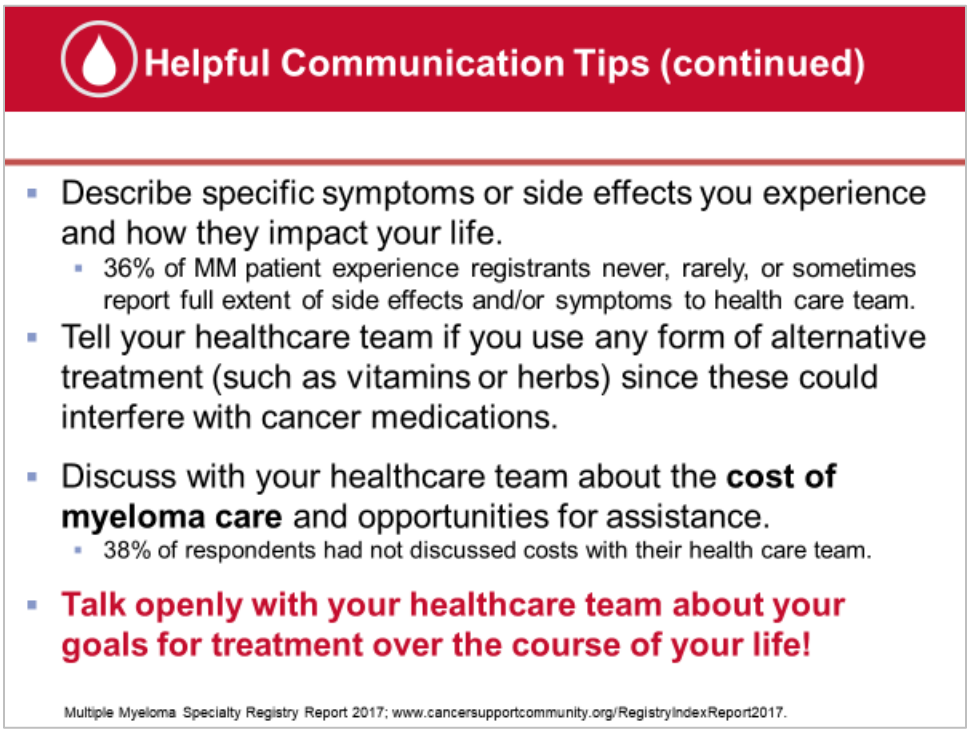
Also, ask your doctor, what are the goals of the treatment? We have so many options these days. What is the goal of treatment? What's the best therapy for me given all these different options of clinical trials that are available? And if you don't understand, ask again. These days in medicine, doctors and providers are pushed to see more and more patients in a limited amount of time. So, you need to be able to stop your doctor and provider and say, "I want you to explain that again." You are empowered to do that. I want my patients to do that. If they don't understand, stop me and ask me again, explain it again because it is important that you know what's going on with you. It's also important for you to know what are your goals of therapy. Do you want to wipe the cancer out and are willing to accept lots of travel for IV therapies or you just want to keep it under control? And, actually though, do you have enough information to make an informed decision because you are the star of the show. It's not your family, it's not your doctor, you are the star of the show; and you need to take an active role in decision-making for yourself because there are so many options for treatments these days.



Also, find out how does your doctor/provider like to communicate? Make sure that you feel respected by your team. If you don't feel respected and don't feel listened to, move on to another hematologist/oncologist. Always ask for a second opinion about the diagnosis and treatment from a myeloma specialist who can have access to all the different clinical trials.

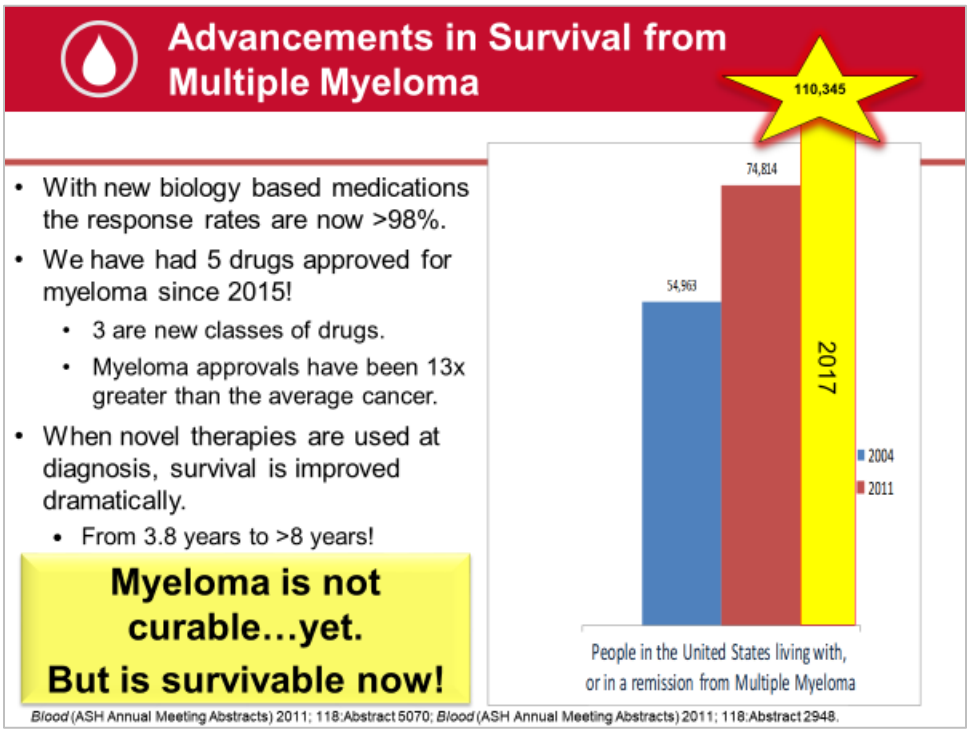
Also, keep a list of your questions and ask your doctor about clinical trials. Always bring a friend or relative. Every time I go to the doctor, I just can't remember a thing because I get so nervous when I visit my doctor. Ask your doctor to take notes or record the conversation. I absolutely allow my patients to record conversations with me.

And ask for help from your healthcare team in gathering information. In a study that was done asking myeloma patients about their experience, 88% of myeloma patients felt that it was important to get help gathering information before their meeting with their doctor. So, these patients were long-term myeloma patients; and when asked what would you do if you had to do this all again, 88% of them said that they would want to have information before they visit their cancer specialist, and 83% said it was important to have a written list of questions when you go to your provider. Very important in participating in the care.



Just make sure you describe your symptoms that you experience. We found in a study that 36% of myeloma patients won't tell us what their side effects are because they think that we won't understand or providers can't do anything about it or they're afraid that there aren't any other treatment options available. There are lots of treatment options available, and we can help with the side effects. But please make sure that you communicate your side effects. Tell your healthcare team if you use any alternative medications because they could interfere with myeloma medications, and discuss with your healthcare team the cost of care of your myeloma.

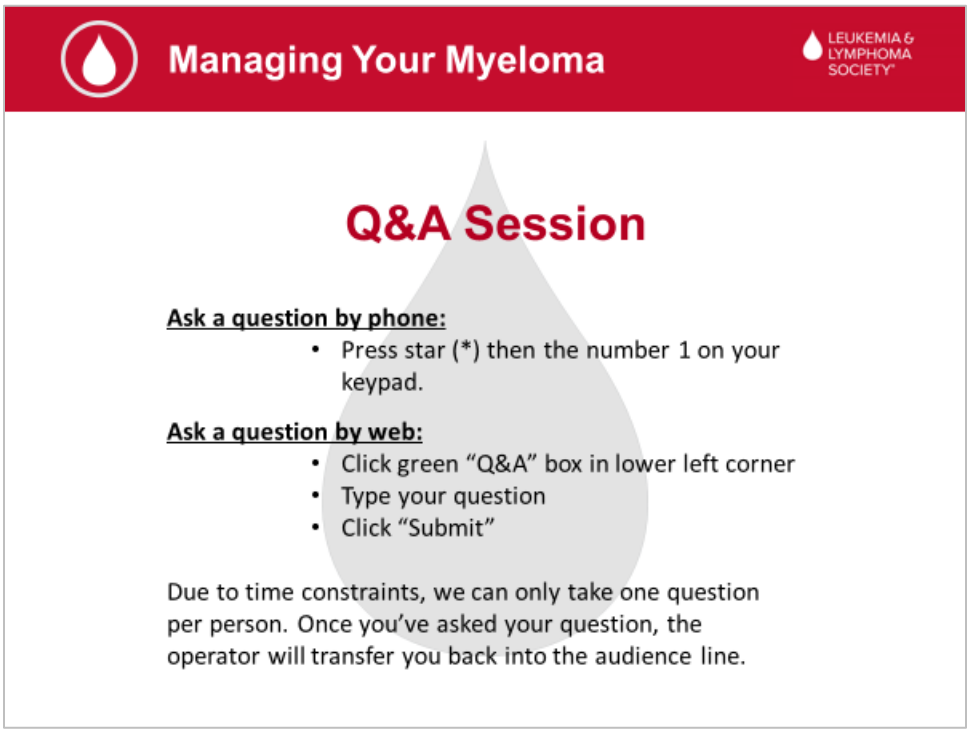
Thirty-eight percent of patients will not discuss their cost of care with their healthcare provider. We can help with that. LLS can help with the cost of care, just make sure that you ask us; and talk openly with your healthcare team about the goals of therapy that you have.



So, in conclusion, with the new biologic therapies, and especially the new immune therapies combined with the biologic therapies, response rates are now over 98% for newly diagnosed patients. And I showed you two studies that were hovering at 100% response rates. Unheard of. When I was an intern, that number was 30%. Now it's 98% response rate. We had just five drugs approved for myeloma since 2015, and that is three new classes of drugs and that is 13 times more than your average cancer. We are well ahead of the curve in finding better treatments for myeloma and the strive to cure this disease.

And the remarkable thing is if you look in 2004, there were only 54,000 people living with myeloma. In 2011, that rose to 74,000 people living with myeloma. That is 20,000 more people that have myeloma in the United States. Why? Because 20,000 more people had survived the disease between 2004 and 2011. And then when you look at now, 110,000 patients living with myeloma in the United States when it was just 47,000 a few years ago. That is remarkable.

And when we use these novel therapies, now the survival has improved dramatically. So, myeloma is not curable yet, but it is survivable now; and we are definitely working on the cure. Thank you.



QUESTION-AND-ANSWER SESSION

Lizette Figueroa-Rivera, MA

Thank you so much, Dr. Cole, for your very clear and informative presentation. It's now time for our Question-and-Answer portion of our program. We'll take the first question from the Web audience. Wanda and Jan are asking about smoldering myeloma. Jan is asking what are your quarterly or yearly follow-up procedures, and have the odds changed at all for the progression from smoldering to active myeloma?

Craig Emmitt Cole, MD

That's a great question, and smoldering myeloma has been one of the real hot areas in myeloma, especially with all the new therapies that have come out for multiple myeloma. The standard is that we do a risk assessment at the time of diagnosis—how high are the light chains, how high are the proteins and how high are the plasma cells inside the bone marrow? And then, again, we follow the protein level to see if there are any changes through time. So, we usually do all the same tests that we do for multiple myeloma every month for three months is kind of our policy here at the University of Michigan—I think kind of standard. And then after three months, if regular follow-ups don't show any change, we then start moving to every three months doing the same test by making sure we tell the patient that if there are any changes in energy, because fatigue is such a common presentation of multiple myeloma, if there are recurrent infections where you have three bad bacteria antibiotic-requiring infections in a short period of time, or if there's any new pain, to give us a call.

But the standard of care in the United States is currently observation because overall about 10% of patients will turn into multiple myeloma. But there are a lot of clinical trials going on in order to (a) figure out which patients have mutations that are more likely to turn into myeloma, so we can act early and (b) what are the right drugs and low toxicity drugs we can use for smoldering myeloma. So, I recommend that for patients who are smoldering, that they should also get a second opinion these days because there's (a) opportunities for clinical trials and (b) it is really an emerging area in myeloma.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Valerie from Illinois. Valerie, please state your question. Your line is now live.

Valerie from Illinois

Yes, Dr. Cole, is it possible to get new lesions while you're considered MRD (minimal residual disease)-negative or in remission?

Craig Emmitt Cole, MD

That is a really good question because the MRD measurement is fairly new, and so some of the details about MRD measurement, especially outside the bone marrow, isn't really clear to us because although the bone marrow may not have disease in it, there could be rests of disease elsewhere. And, in general, it's unlikely to develop new bone lesions; but we're not 100% sure of that.

And one thing is that the x-rays that we use to follow the myeloma, those x-rays are 117 years old; and sometimes patients can be in a remission, but the bone lesions don't disappear. But certainly, when under close follow-up, it is unlikely to have a new lesion. And usually if there's a new lesion, we need to confirm that with one of the better, more sensitive tests.

Lizette Figueroa-Rivera, MA

Thank you for the question, Valerie. The next question comes from our Web audience. Connie asks, "Is it true that multiple myeloma affects African Americans twice as much as other ethnicities; and if that is true, is there specific research focused on determining why as well as developing treatments that specifically target the effects of the disease in this population?"

Craig Emmitt Cole, MD

Yes, that's a great question. They're all great questions. But, yes, people of African descent, in fact, the incidence of myeloma in general is broken up by ethnicity. People of African descent have the incidence of 12.5 people out of 100,000 people. So, they'll be 12 in 100,000 African American people that will have myeloma, while the all races, the general incidence is 5 per 100,000. So, yes, it is double the amount. In people of Asian descent actually have about 3.5 to 4 per 100,000. So, people of Asian descent and Native Americans have a lower incidence of myeloma. Caucasians and Hispanics are in the middle at about 5 per 100,000, and African Americans have 12 per 100,000.

And you are absolutely correct in that one thing that is another hot area of investigation is to see what is the difference in ethnicities in this disease. There's some strong hints that Caucasians are more likely to get high-risk disease and African Americans are more likely to get low-risk disease. Of course, that's not across every single person; but there are some trends of grouping that we're beginning to see.

And, yes, the two-pronged attack and seeing this is that there's a clue there about ethnicity in myeloma, a clue that they may be different diseases, that they may be remotely related diseases and may benefit from either more therapy for some ethnicities and risk values or maybe even less therapy for those ethnicities that do especially well and have low-risk disease. So, one thing that we're striving towards is trying to figure out the different types of myeloma. Right now, we treat newly diagnosed myeloma with one therapy generally, RVD. We need to be able to distinguish between the different types of myeloma and study those independently to find the best therapy for each group of myeloma. So that is really a very hot area and a very exciting area of research.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Kathleen from New York. Kathleen, please state your question. Your line is now live.

Kathleen from New York

Hello, I have kappa light-chain myeloma and I've gone the gamut of all the chemotherapies and I'm now on dara (daratumumub). I've been on it for now 12 months. My numbers were good, but in October the kappa went up to 8.31, the lambda 0.47, no ratio. In December, kappa went up to 10.45 and lambda 0.49, and the ratio was 21.33, which is high. And this month the kappa went up to 15.85, lambda 0.56, and ratio 28.30. I'm concerned that pretty soon my numbers will be over, the kappa 19.8 and there are no clinical trials in my area. I only take the dara with prednisone. I don't have any other chemos with it. What should be my next choice?

Craig Emmitt Cole, MD

One thing is I would recommend getting a, this is a perfect point for a second opinion from a myeloma specialist; and the reason I say that is there was a slide that I had somewhere along the line that had all the different therapies for myeloma that has relapsed. And we used to have two or three different therapies, but now we have a lot. And including decisions of what to do with the dara or switching to the other antibody elotuzumab which does work fairly independently of daratumumab or using one of the other newer therapies such as carfilzomib or Ninlaro.

But what I usually recommend is that there's so many choices these days to kind of go through that seeing a myeloma specialist and getting a clear idea of what's available to you and what are the options. When I sit down with a patient, I usually write down the general categories of treatment for a relapsed myeloma. IV plus pills, all pill therapy, and/or aggressive therapy. And so, I would recommend getting a second opinion and going through some of the multitude of options.

Lizette Figueroa-Rivera, MA

Thank you and, doctor, the next question is from Marva and John. Both are asking about diet and nutrition. Are there any foods they should be staying away from, what's safe, are diet foods okay, as well as sugar?

Craig Emmitt Cole, MD

My wife's a dietitian. We talk about this at dinner sometimes. So, there are, actually, in the past year, past couple years, there's been actually more and more information about this. And so, one point is that obesity, just recently, obesity or body fat and outcomes from myeloma are now related, both in the incidence of myeloma and in the survival with myeloma. So, the prednisone, you know, and the dexamethasone, can make you gain weight; but it's important to eat a balanced diet of fresh fruits and vegetables, limited process foods, and limited complex carbohydrates. So, the vegetable counter and the fruit counter are your better options than going to a fast food restaurant, or fast food place to get an apple pie. A whole apple is better.

For the food to stay away from, one in particular is on the day that you receive Velcade or bortezomib or Ninlaro, that green leafy vegetables or green vegetables like broccoli taken the day of Velcade therapy or Ninlaro therapy could interact with those two drugs specifically. So, we usually tell people to, they can eat salads every day, except for the day that they receive the Velcade or the Ninlaro. But it's important to have a balanced diet because there are macro nutrients inside an apple that you can't reproduce in a pill or get destroyed in an apple pie—and I love apple pie.

Lizette Figueroa-Rivera, MA

I think we all do. Thank you, doctor, and we have our next question coming from the telephone audience please.

Operator

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

Richard from New Jersey

I've been in remission three times over the last nine years, and the latest remission was due to an infusion of dara with Pomalyst. And since they took me off all the drugs, I'm experiencing a lot of side effects, like pains in my hand which they say it could be carpal tunnel. I wound up in the hospital for 44 days and rehab because of *Legionella* pneumonia, a gallbladder infection, blood clots and whatnot; but I'm okay. They didn't treat any of these problems because of the blood thinners that I was on like Xarelto (rivaroxaban) and aspirin and whatever.

So, I don't know, it's one good thing to be in remission; but now I'm going through a lot of side effects. Is that common?

Craig Emmitt Cole, MD

The antibodies are known to have some immunosuppressive effect, so people do get some increase in infections when they're on these treatments. But the one thing to really kind of think about is that a lot of those symptoms can be from the treatment, but they really can be from having the myeloma returning. And so, I think that, especially having new blood clots is something that can happen when patients have recurrence of the myeloma coming back. That really doesn't happen with the antibody therapies.

And the one trick that we're kind of finding out is that patients that receive the antibody therapies, sometimes the myeloma can come back in kind of a sneaky way. It can come back without bone lesions but lesions in the soft tissues. And especially they can come back not producing as much protein as they used to. So, the longer that patients have myeloma, the incidence of having no protein being produced by the myeloma cells goes up.

And so, I think that when somebody has recurrent infections and blood clots, the first order of business would be to make absolutely sure that the myeloma's not returning in some kind of sneaky way. And then the second thing is to see if there's any way to curtail the infections, and sometimes patients will have low normal antibody levels while they're on these drugs; and sometimes they can benefit from antibody infusions to help boost their immune system. And the antibody infusions are called intravenous immunoglobulin or IVIg. And sometimes when patients have recurrent infections on these therapies and their myeloma is totally controlled, we'll give IVIg infusions. But I would just make sure that it's not recurrent disease.

Lizette Figueroa-Rivera, MA

Thank you. And the next question from the Web comes from Anthony. He's about six months post-transplant, and he's asking if he should use a mask when he travels on airplanes.

Craig Emmitt Cole, MD

So, I would. And the good thing about masks on airplanes is that the big thing that it does is it keeps sick people away from you. They see the mask, and they're like, "Gosh, I'm sick. I don't want to get sicker," so they kind of go the other way.

But airplanes are such a hive of close quarters and infection that it's probably not a bad idea to wear a mask. But especially it helps to keep people at arm's length because a lot of these infections are transmitted by hand contact and sneezing or coughing on people.

Lizette Figueroa-Rivera, MA

Sure, thank you. And our next question from the Web is from Patrick. "If you get diagnosed at age 45 or younger and 90% bone marrow and 10% circulating in the blood, does that mean it'll be aggressive?"

Craig Emmitt Cole, MD

So, age isn't so much a discriminator of aggressiveness. It kind of feels that way because it's a bit unusual to have myeloma occur at a young age, but we've had patients that are as young as 18 and as old as 99 come in with myeloma.

Having the circulating plasma cells, that is a sign of aggressiveness because the plasma cells should be pretty much confined to the bone marrow. I mean that's their kind of gig is that they're very dependent on being attached to the bone marrow stromal cells or to the osteoclasts inside the bone. And for them to have figured out a way around living inside the bone marrow, that they have some independence means that they could be a bit more mutated and be a bit more tricky in treatment. And so usually we do consider those people with circulating plasma cells higher risk and usually are ready to open up the playbook for those patients.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Mary from Ohio. Mary, please state your question. Your line is now live.

Mary from Ohio

Doctor, I'm on Ninlaro and dexamethasone weekly and also on Pomalyst, 14 days on, 14 days off. But the cancer is still growing, so now they have me on an immune chemo treatment, so does that sound good to you?

Craig Emmitt Cole, MD

I think absolutely. A lot of those clinical trials that were in the slides, the response rate for adding the immune therapies on is boosted up or is supercharged by using the immune therapies. Sometimes, especially if there's side effects, sometimes you change up the therapies; and so, if someone's on pomalidomide or a Pomalyst-Ninlaro-dex and they're relapsing, sometimes we'll change the therapy to using Revlimid again or Velcade again or carfilzomib. But I agree with adding on the immune therapies. They boost almost every therapy that we have for myeloma.

Lizette Figueroa-Rivera, MA

Thank you. And we'll take the next question from the Web. Katie's asking, she had a transplant four years ago and she's still on Revlimid maintenance. How long should she continue?

Craig Emmitt Cole, MD

That is a fantastic question. So, we don't know yet, but we recommend that people stay on Revlimid maintenance for at least one to two years. And then it really is looking at are you having side effects from the Revlimid that are interfering with your quality of life. When you're on the induction therapy, the RVD and the transplant is like flying in a propeller plane. You can tolerate it for a while because it's not a long flight. But maintenance therapy is like going on a coast-to-coast airline where you've really got to make sure that your flight's comfortable because it's a long treatment.

And so, the maintenance therapy is usually limited by patient tolerance, and so make sure that you talk to your provider about any side effects you're having from the Revlimid because they're amendable by sometimes dose adjustment, and there are medications that can help, especially with the diarrhea associated with Revlimid maintenance. But definitely don't suffer with the side effects of the Revlimid maintenance or any maintenance therapy. Make sure you discuss that with your doctor because there are a lot of other options for maintenance.

But the short answer is that we have people remain on as long as they want to, but also realizing that there's a hot area of research for maintenance therapies; and there are going to be lots of changes

coming in the near future in what we use as maintenance therapy and who receives maintenance therapy. So, it's important to stay current with the new things that are happening in maintenance therapy right now.

Lizette Figueroa-Rivera, MA

Thank you, doctor, and the next question from the Web is from Jack. Jack's asking, "Are there polyclonal antibodies constructed to attack multiple antigens?"

Craig Emmitt Cole, MD

Yes. There are the BiTE (Bispecific T-cell Engager) antibodies or the bispecific antibodies which are really, really exciting. And what they do is that some of the BiTE antibodies have receptor for myeloma cells. They also have a receptor for the T-cells, and these antibodies actually bring, in the same way that the CAR T-cell therapy does and how the mono antibodies, the uno-specific antibodies like dara and elo (elotuzmab) don't do, that they bring the infantry. They bring the soldier right to the doorstep of the cancer cell by being bispecific, that they bring the T-cell right to the myeloma cell because the antibody has two heads on it. Then the T-cell can destroy the myeloma cell on site, because sometimes what happens is that the myeloma cells are protected and have a cloaking device which makes them invisible to the immune system. And so that's a real trick that myeloma cells use to stay alive is that they have a cloaking device. If we have a bispecific antibody, then the cloaking device doesn't work, that it brings the T-cell right up against the myeloma cell and then they duke it out and the T-cell always wins.

Lizette Figueroa-Rivera, MA

Thank you, Jack, for the question and thank you, doctor. And our last question today, doctor, comes from Catherine. She's asking, "What about chemo fog or moodiness as a chemotherapy side effect? Can that be experienced with myeloma drugs?"

Craig Emmitt Cole, MD

Oh, yes, and especially with the moodiness that's related to the steroids. The dexamethasone can definitely do that.

But one really important thing is that sometimes chemo-brain, forgetfulness, sleep disturbances can be signs of depression. And in the study that we did in surveying myeloma patients, we found that myeloma patients have a higher likelihood, I think it's number five among the different types of cancer, and the highest of the blood cancers that are associated with depression. And depression can have exactly those same symptoms of moodiness and forgetfulness and lack of concentration and lack of wanting to engage in activities. And the good thing about depression is that it is very treatable, and there are lots of very good therapies for depression.

And so, given the higher likelihood of depression in myeloma patients, it's important to not just, because the treatment can definitely do some of those things, but make sure it's not depression. Ask your doctor about depression because another thing that we found out is that most patients will not discuss how their mood is, or if they're depressed, with their provider unless the provider asks. Don't do that. Don't wait for me to ask if you're depressed. If you suspect you're depressed or your family suspects you're depressed, ask that right out because we want to treat that and we can treat depression associated with myeloma.

Lizette Figueroa-Rivera, MA

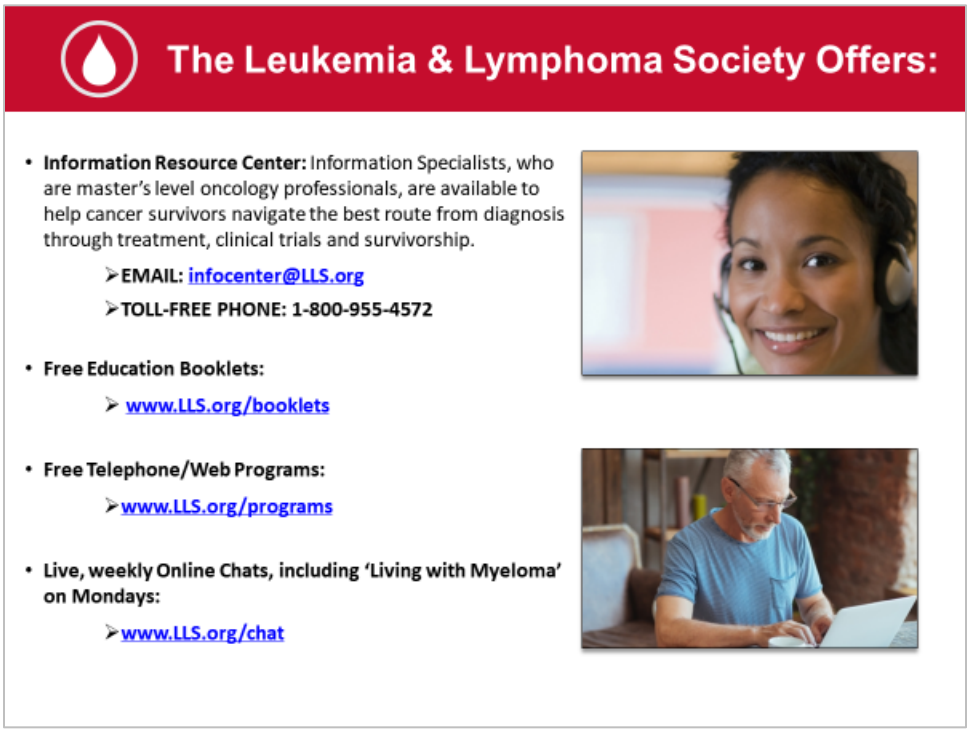
Well, thank you, Catherine and thank you, doctor.

Dr. Cole, thank you so much for your continued dedication to patients; and you and your colleague's research successes have really made a positive impact on people's lives.

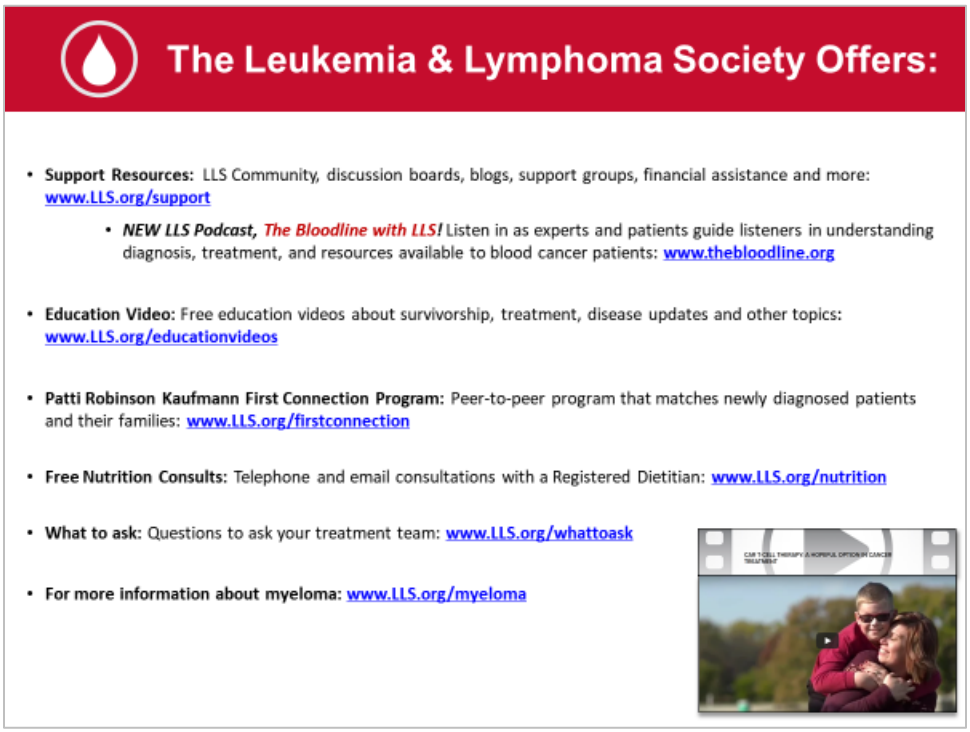
CLOSING REMARKS

Lizette Figueroa-Rivera, MA

If we didn't get to your question today, you can call The Leukemia & Lymphoma Society's Information Specialists at 1-800-955-4572.



Information Specialists are available to speak to 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 treatment.



Again, we'd like to acknowledge and thank Amgen, Bristol-Myers Squibb, Celgene, and Takeda Oncology for their support of this program. And thank you, Dr. Cole, for sharing your knowledge with us today. To all of 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.