A Comprehensive Look at Myeloma Treatments and Testing

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Jack Aiello:
Thank you very much. I am excited to be here in Houston and hosting this meeting, Understanding Multiple Myeloma: A Comprehensive Look at Emerging Treatments and Testing.

Does your loved one have myeloma? Do you have myeloma? Are you living with it? Would you like to connect with others? If so, you've tuned into the right place.

As indicated, my name is Jack Aiello. I was diagnosed with myeloma nearly 25 years ago. So, I have appreciated all that I have seen in the world of myeloma and all that has occurred, and so many treatments that are available now that weren't available before. I'm excited like you to keep learning about what's new and what's emerging.

Just some ground rules—remember, the opinions expressed during this program are not necessarily the view of the program sponsors or our partners. Our discussions are not a substitute for seeking medical advice from your own doctor and please, talk to your own doctor in terms of what's most appropriate for you.

I want to thank our partners also. Our partners are The University of Texas MD Anderson Center, which is where we are here, an organization called Myeloma Crowd, and another organization based out of Houston called CanCare. The town meeting is sponsored by Janssen Biotech, Karyopharm Therapeutics, Takeda Oncology and Foundation Medicine.

So, I'm curious, at least with the inpatient audience here—how many myeloma patients are in here? So, a quick snap tells me about 40 or 50 patients. How many myeloma patients have been diagnosed less than two years? So, maybe half of those. And how many have been diagnosed more than five years? So, you one to two-year folks, you go sit next to those more than five-year folks, because you'll have stuff to learn from them.

I think it's always imperative for us to learn as much as we can from our doctors, from our fellow patients, from support groups, which are available online. There are also several support groups here in the Houston area. It's imperative for us to learn as much as we can.

So, to let you know what we're going to cover here today, we're gonna talk about myeloma treatment and research that's going on. We're gonna look at targeting myeloma through the labs we all go through many times. And what's it like to manage day to day life with myeloma? How can I empower myself? We'll get to a Q&A session.

We're gonna drill down on these topics with experts on hand. So, now, let's meet our panel. I'm actually gonna start with the most important folks. In the front row here, we have Beth and Merlin Moseman. Merlin was diagnosed about seven years ago, I think. He and she will be sharing more about their experience after our break. I look forward to both meeting you and asking you questions.

We also have Carl Burgman, who I got a chance to meet last night. You will also get to learn more from him. We have Thomas Verm, our social worker, who will be on stage after break as well. And we have Dr. Pei Lin, a hemapathologist and my first question to her will be, "What's a hemapathologist?" So, we'll move on from there.

On stage with me, I'm really pleased to introduce—more of you know her than me—Dr. Krina Patel, who's Associate Professor here at MD Anderson, and Dr. Sagar Lonial, who I've known for many years at Emory. Dr. Patel, give me your one word, one sentence answer in terms of what excites you most about where we are now with myeloma.

Dr. Patel:
Sure. So, I started research in myeloma eight years ago. I became faculty five years ago. I'm a little bit newer. But I got to join right when all of our therapies starting growing exponentially. We have these new therapies coming out every year now. So, being on that exponential curve is sort of the most exciting part for me.

Jack Aiello:
Yeah. And, Dr. Lonial, I know you've been in this business for a little bit. Tell me what excites you about where we are now.

Dr. Lonial:
Yeah. It's interesting. I thought when I started we had new drugs with bortezomib (Velcade) and thalidomide. So, I think what really does excite me is the context that we have a lot of tools now that we didn't have 20 years now. I think we can start to introduce the word cure in subsets of patients with myeloma. And if not cure, then long-term control. That to me is really exciting, because we haven't been able to really do that for a long time.

Jack Aiello:
So, to kick things off, we're gonna actually watch a video by Elisabet Manasanch, who's here also at MD Anderson. She's gonna be discussing some of these newer emerging therapies for myeloma. She'll cover a lot of information. So, our inpatient panel will then go into further detail about it. You can follow along with the drug names she will mention. There are handouts you have. With that, let's start the video.

Dr. Manasanch:
Well, there are a lot of things coming out of new therapies that we actually got some data for the first time at the annual meeting of the American Society of Clinical Oncology, which was in June. So, we actually got for patients who have relapsed/refractory myeloma, there are a lot of new therapies. One of those therapies is called iberdomide. It's a new immunomodulatory drug.

So, it follows in the steps of thalidomide (Thalomid), lenalidomide (Revlimid), pomalidomide (Pomalyst) and now, iberdomide. It seems to have activity in patients that no longer have response to immunomodulatory medications, including thalidomide. So, this is some promising medication that is certainly gonna need more clinical trials. That's something that patients can look forward to if they have the need for those medications at this time.

Additionally, there's been another approval from the FDA based on an isolated program for a medication called selinexor (Xpovio), which is a tablet that is taken basically a few times a week and that's taken with dexamethasone. That's what the approval for. So, this medication called selinexor with dexamethasone (Decadron) is also a new class of medication.

So, it's not a proteasome inhibitor or an immunomodulatory drug. It works through basically getting some of the proteins that work in sterilizing the neutrons of the cell. So, you can get that medication also through your doctor that's approved. So, if you don't have a lot of treatment therapy, that's something that you can do.

Of course, there's also other medication called BiTE, the biospecifc T-cell engager. Those are antibodies. These antibodies are in clinical trials and we also have some clinical data for the first time in the past few months showing that they're also responsive in patients that don't have a lot of other good treatment options.

So, if you're one of those patients, you can go for either iberdomide off clinical trials, selinexor that you could get just with a doctor in the community or off a clinical trial. Then there's this BiTE medication, which are also in clinical trial and are ongoing.

Of course, there is also all the clinical trials with CAR T-cell therapies. One of the new things is that there's going to be soon a study opening that has what we call off-the-shelf CAR T, which means they use T cells. These are white cells from other people. They're not your own T cells.

So, they can manufacture those cells very quickly and I think most patients know already about CAR T-cell therapy but that's some of the new things that are coming in that phase. On top of that, there are still ongoing studies with CAR T-cell therapies.

Additionally, there's been a new CD38 antibody. It's called isatuximab that has shown in a randomized study with thalidomide and dexamethasone that there is basically the time that patients don't relapse increased. So, there's a new CD38 antibody that is not daratumamab (Darzalex) that is probably maybe approved by the FDA later this year or next year. So, that's another CD38 antibody that is probably gonna be available soon, again, off clinical trials.

Another important thing—there are some clinical trials ongoing for newly diagnosed myeloma. Most of these studies, what they're doing is they put a proteasome inhibitor with an immunomodulatory drug with dexamethasone, and then they add an antibody. So, they do a lot of studies comparing the addition of these antibody with the usual backbone of myeloma therapies for newly diagnosed patients.

So, those studies are ongoing. If you have newly diagnosed myeloma, that's something that you can participate in. So far, the initial report shows that there seems to be more efficacy if you do the four drugs versus the three drugs, which is what we've traditionally been doing.

And then if you have a smoldering myeloma, there's a lot of evidence—right now, there are a few randomized studies, all of them showing that if you do treatment a little bit earlier on that there seems to be a delay in the onset of multiple myeloma.

However, we have not yet agreed on what is the best therapy to give and there are right now, for example, there are studies ongoing, probably there's gonna be another study for patients with using antibodies.

There's one right now ongoing, daratumamab versus observation, which patients can enroll into and there's another one probably also with daratumamab with lenalidomide-dexamethasone. There might be another one also, maybe isatuximab with lenalidomide-dexamethasone.

So, those patients that have smoldering myeloma, even off clinical trial, we're not certain, we don't have a formal recommendation, they can go on clinical trials for that. It seems that just doing treatment early does impact the disease in a favorable way.

Jack Aiello:
So, that was pretty—a lot of information there in five minutes. Let's talk a little bit more about that. I'm gonna use this as a jumping off point. I want to do it in reverse order that she spoke about. So, let's begin with smoldering myeloma. I think she was really referring to high-risk smoldering myeloma.

So, Dr. Patel, can you help us understand what smoldering myeloma is and how is high risk determined? We use high-risk in multiple myeloma as well, but they are different.

Dr. Patel:
Sure. So, of course, unlike other cancers, there are maybe a few other cancers where we detect early precursors for myeloma, MGUS to smoldering to actual myeloma that needs treatment.

In 2014, some of our rules changed of what's considered smoldering versus actual myeloma. It used to be the CRAB criteria, where you had organ involvement. In 2014, we added light chain ratios of greater than 100 or if you had MRI changes, specific MRI changes, we would say you have myeloma and now, you need to start treatment. So, smoldering changed.

What we were trying to find out is how do we find patients who have high-risk smoldering, meaning that their likelihood of becoming symptomatic myeloma in the next two years is high enough that we want to treat them before they actually get organ involvement or problems. So, one is quality of life. We don't want people to get broken bones before we start treatment if we can help that.

Second, if we can prolong life, of course, that's where we think maybe this idea of cure, eventually we can do it before people have any problems. I think there have been multiple different ways of looking at what high risk is.

There are criteria like the Spanish criteria, where they include looking at flow cytometry of the bone marrow biopsy, but not everywhere can do that. It's a little bit hard. It's a harder technique to make sure everyone gets the same answers.

So, what was presented at ASCO recently and it's something that's been looked at—it was using the 20/2/20 rule. So, if you have 20 percent in your bone marrow, even though it's smoldering—remember, 60 percent or higher means that you actually have active myeloma, that we would start treatment, but between 10 percent and 60 percent is considered smoldering.

So, now, if you have 20 percent to 60 percent, that could be a risk factor. The other two is if you have more than 2 grams of the monoclonal protein that we look at. Then the third is 20—the light chain ratio. If your ratio is greater than 20—remember 100, you're automatically considered as myeloma. But if it's greater than 20, those are the three risk factors we look at.

If you have two or more of those when you're diagnosed as smoldering, we now consider that high risk. It's about a 49 percent to 50 percent chance that in two years, you're going to have active myeloma that needs treatment. So, the question is if we intervene early, does that change outcomes for those patients?

Jack Aiello:
So, Dr. Lonial, can you summarize what trials are telling us now about high-risk smoldering myeloma?

Dr. Lonial:
Well, you know, the trial landscape is pretty broad. There are lots of trials that have gone from low-intensity therapy to something involving triplet or quadruplet induction, two transplants, and three years of maintenance for patients that fall into high-risk smoldering.

I think it's important to recognize that there really are only two randomized trials that have been completed in this setting. Both of them compared early therapy with observation. Now, the Spanish trial is much older and has much longer follow-up than the US trial, but that trial also had some issues with it. I think the flow cytometry piece that you mentioned is a concern. They used regular X-rays as an entry criteria for that trial.

So, one of the concerns I that perhaps there were patients that we would now call myeloma based on MRI or PET scan that may have been included in that trial. But nonetheless, it showed a longer remission duration or longer time to developing myeloma and they showed a survival benefit for the use of early therapy. But those weaknesses limited widespread adoption.

So, at ASCO this year, I actually reported data on the largest randomized trial ever done in smoldering with lenalidomide alone versus observation. We demonstrated the same magnitude of benefit that the Spanish showed. In fact, if you take that 20/2/20 group that you described as the high risk, there was a 90 percent risk reduction of developing myeloma within three years by using just lenalidomide alone.

So, at least in our view and at least the conclusion in the manuscript that was accepted two days ago says that we recommend that for patients that are high risk if they're not gonna go on a trial or they can't get on a trial that early therapy with either len or len-dex is a standard of treatment approach.
Now, I think there are a lot of investigations. There are doublets and triplets and all sorts of complicated trials, but until we demonstrate that those trials are better than our current standards, I think it's hard to say we should go with more intensive therapy than just lenalidomide alone or lenalidomide-dexamethasone.

Jack Aiello:
So, based on that paper, at least you and Emory and folks are recommending that high-risk smoldering patients be treated or at least be offered that option.

Dr. Lonial:
Yeah. We would want people to enroll on the current ECOG trial. The ECOG trial is lenalidomide-dexamethasone versus daratumamab-lenalidomide-dexamethasone, which addresses that question of more intensive therapy.

But I think the ideas that treatment in the context of smoldering has to show a survival benefit misses the fact that if you prevent organ damage, that's a big deal. If you prevent a fracture, if you prevent the development of bone disease, if you prevent renal failure, that's a huge deal.

With myeloma patients living 8, 10, 12, 25 years, the idea that you're gonna see a survival benefit in our lifetime for a randomized trial is pretty low. So, I think we need to be comfortable with the idea of reducing risk and improving quality of life.

Jack Aiello:
Quality of life is so important. And you would agree, Dr. Patel?

Dr. Patel:
So, I definitely discuss it with all of my patients. I'm gonna give a little bit of controversy to this, but I agree. I think this is the best trial we can now use as backbone to compare all our other trials. If there are trials, we try to get patients—and Dr. Manasanch actually does most of our smoldering trials.

However, on the flip side, if you say 50 percent of patients are likely to get myeloma in two years, what about the other 50 percent? So, do I have patients that fit that high-risk criteria that are nine years going without any treatment and still doing well. So, that number to treat, that number needed to treat to help patients, I think our goal is to get better at figuring out what high risk really is and I do think we need better ways to say someone is high-risk.

Once we have that, then yes, then I think all those patients should be treated. When we don't have—it's still a 50-50, I talk to my patients and I tell them based on this data, recommendations would be to start treatment. However, let's talk.

Then we decide if it's the right thing to do or not. The other question is are we gonna have more resistance? What do we do when someone relapses again? Then what treatment do we do? All the trials we're doing now will give us those answers in the future. So, yes, we definitely discuss it.

Jack Aiello:
So, let's move on to newly diagnosed myeloma patients. Dr. Patel, Dr. Manasanch spoke about possible four-drug therapies, perhaps adding a fourth drug such as Darzalex, also called daratumamab, to the triple regimen of Velcade, Revlimid and dexamethasone. Can you comment about this approach?

Dr. Patel:
Sure. So, we always—our goal is to get the best response at the beginning. So, when we start treatment, if I can't cure yet, our goal is to knock the myeloma down when it's the—I call it the dumbest, when it hasn't seen any drugs yet—we know we can work the best. The better the response we get, what we call a deeper response, we know the patients do.

One of the biomarkers we use for this right now is something called minimal residual disease. We know that the patients who get into minimal residual disease and stay there for at least a year, the myeloma hibernates a lot longer. So, our goal is to get as many patients to that state as possible when we start treatment.

I think there are patients who get to that with our triplets. So, the question really is adding a fourth drug, which patients is that going to help to get into that state? More of our patients can get into the best response and have the longest hibernation or progression-free survival, then yes, we want to add that fourth drug.

Now, we have early response rates from the GRIFFIN trial, which dara with VRD. I think they're gonna present it soon. I think by ASH, we will have the rest of the data that really tells us, "Is there a specific patient group that we actually help or does this sort of help everybody?" We've done trials with four drugs before, before I joined myeloma, but with Cytoxan, Velcade, Revlimid and dexamethasone.

There, unfortunately, toxicity was much higher and we didn't see a better response. I think this has a much better chance. In terms of toxicities, we have to see the long-term data. I do think there's a group of patients who have high-risk myeloma, for instance. I'm hoping that four-drug really does help those patients.

Jack Aiello:
So, Dr. Lonial, Darzalex or daratumamab has made its way to frontline therapy. I guess if there were a standard induction or first line therapy today, it would be Velcade, Revlimid and dexamethasone. But Darzalex, Revlimid and dexamethasone, is also being used. How do you decide which one?

Dr. Lonial:
So, I think the discussion that Dr. Patel had in terms of the benefit of four drugs and a goal of trying to achieve deeper responses earlier on is really important. So, the idea of de-escalation of therapy and going from what we may think about as a four-drug regimen to a three-drug regimen really needs to be demonstrating that the efficacy not just as measured by MRD, because I will tell you, I'm a little bit skeptical of MRD early on. But I think that needs to be measured by PFS.

So, if there's a question of frailty, if there's a question of performance status, then I'm comfortable saying maybe three is the better option. But if you've got a young fit patient—there's no age limit to young and fit in my view—it's really all about functional status.

I've got a 78-year-old that had a transplant, was walking 18 holes of golf a month later. I've got a 50-year-old that I said no to. So, I think it really is about function. I want to give them what I think is the best early therapy to achieve the goals that Dr. Patel described.

Jack Aiello:
And if I'm debating among the two three-drug regimens, RVD or Darzalex-RD—how do I decide or what do you recommend or is there a recommendation?

Dr. Lonial:
Well, I think the data we have on DRD, daratumamab with lenalidomide-dexamethasone, is really based on a very different patient population than the trials that have looked at RVD, which tend to be a mixed back of both younger and older patients, at least from the SWOG study. So, I think it's hard to say that the answer is X or Y.

I think you have to make a decision. If there's a patient that has high-risk disease, I'm gonna be a little hesitant to use daratumamab-lenalidomide-dexamethasone as their induction alone, because we know that the proteasome inhibitors are so important in their outcome. So, it's a little bit more subtle than, "Do you choose A or B?"

Jack Aiello:
So, let's talk about the relapsed refractory patients, specifically Dr. Patel, let's talk about the one drug that she mentioned was approved, selinexor.

Dr. Patel:
Sure.

Jack Aiello:
Can you say a little bit about the mechanism apparently, which is different than other drug categories that we have and who might be the patient best-suited to take selinexor?

Dr. Patel:
Sure.

Jack Aiello:
Which by the way, if you haven't already learned, goes by the name Xpovio.

Dr. Patel:
So, yes, I'll be honest—I have not used it as of yet. We are trying to get it at MD Anderson. I have lots of patients that we are trying to get it for. The most important part of this drug, I think, is that the trials that used it, when we have patients—as people move on with their myeloma therapies, myeloma becomes more and more resistant.

Daratumamab, having been approved just a few years ago, are patients who have had the proteasome inhibitors, both Velcade and carfilzomib, and they've had their imids, Pomalyst and Revlimid. And then they've had daratumamab and they're relapsed—we call them penta-exposed or penta-refractory, meaning they've gone through our five big drugs.

When that happens, our therapies don't work as well. That's really where we do clinical trials. Those are our vulnerable patients that we want to make sure we get something different to. That patient population was what was tested in in selinexor. They actually had a 30 percent-something response rate, which is great to have many therapies to be that relapsed and refractory to actually have a response.

I think the caveat there is that it can cause some side effects. So, there is a lot of supportive medicine that has to go in with it, especially in the first month. After that, it's actually a really tolerable drug and patients are doing really well with it.

Jack Aiello:
Yeah. Good. Dr. Lonial, Dr. Manasanch mentioned something called iberdomide, which is one of the imids, like thalidomide and Revlimid and Pomalyst. I'm always wondering, this being a fourth IMiD, can you say a little bit more about that drug? I know it's only in clinical trials now, but do you think it will be a drug that might be useful for patients who are no longer responding to those other IMiDs?

Dr. Lonial:
Yeah. So, the answer to your question is yes. At ASCO, we reported on that data, where we demonstrated that in patients who are resistant to pomalidomide, roughly one in three will respond to iber. The old name for iber was CC220. That was the number name.

Jack Aiello:
Catchy.

Dr. Lonial:
So, iber plus dexamethasone or iber alone was clearly effective, even in patients in whom pomalidomide was no longer offering benefits. It appears that some of the immune effects of the IMiD class are actually more potent with iber than they are with pomalidomide or with lenalidomide.

So, I think it's gonna be a great single agent, combination with dexamethasone agent as we're used to with lenalidomide and pomalidomide, but I think it's also gonna be an immune enhancer, as we've seen with those drugs, probably able to potentially partner nicely with antibodies, those Phase I trials are ongoing right now. I think that it's really a very active drug.

I do want to make sort of a quick statement. I think the discussion about selinexor is really exciting. Having new drugs come almost every year, we love that in myeloma, because it makes all of our other oncology colleagues jealous. They don't understand why there's so much good stuff in myeloma. I think it's because of the partnership that you see here today between all the different stakeholders in terms of improving outcomes.

One point that I want to really hit home is that survival in myeloma is linked with access. Access is linked to clinical trials. So, I think when you see centers like the one here or like ours or others in the US, the reason that our patients, I think, in many ways, do have better long-term outcomes is because our patients have access to new drugs and new trials.

There's a whole host of them here in Houston that are changing the natural history of disease. We have them in Emory as well. I think that is really critical to long-term outcomes for patients.

Jack Aiello:
I couldn't agree more. Clinical trials are awfully important. We're gonna get into that discussion a little bit more when we have the other patients on stage as well who have gone through them or are about to go through them.

Dr. Patel, can you help patients understand what these CAR Ts are about? Dr. Manasanch referred to what's called an AlloCAR T. That's even beyond CAR Ts that we know and love so far. So, where are we in the world of CAR Ts? How fast are these CAR Ts going?

Dr. Patel:
Sure. So, CAR T—obviously, what I tell my patients is when we collect your stem cells, we're collecting a different type of cell here. We're collecting T cells. These are lymphocytes that we all have in our body that help us fight viruses and bacteria and all those kinds of things. They have receptors.

So, each of our T cells is made when we're born and things we're exposed to, they have kind of like night vision. They're made for something specific. What we can do is actually take those cells out and unlike stem cell transplant, where the stem cells are just to make sure you have a normal immune system again after melphalan (Alkeran).

Here, we can actually put a new receptor in. We genetically modified the genetics of that cell, that T cell and then we grow them to bigger numbers. Then we give it back after a different type of chemo to help knock your immune system down just for a little bit. Those cells go in and now, you can imagine these are like little army men with night vision.

They can go in and kill just the myeloma because that new receptor we put in is a flag that's on the myeloma cell. So, it can differentiate between your own normal cells versus the myeloma cells. So, now, they're going into the bone marrow. They're going into the other places that myeloma is and they can actually kill. It's like a lock and key.

Once it seems that flag with that receptor, it turns on, it's activated and it kills. It actually dies too and it brings all the other immune cells there through those mechanisms.

So, we've had great data with one of the trials that's gone the farthest. I think there's 47 trials right now between the US and China looking at CAR T. The main flag that we look at right now is called BCMA, B-cell maturation antigen. And the BB2121, that's through Celgene, has kind of gone the farthest. Potentially, we have our first standard of care, which doesn't have to be on trial next year, early next year. So, we'll find out in the next six months or so. But of course, we want to make it better.

So, as of right now, that's not the cure that we were hoping for, but it has shown really impressive results in patients who have already gone through everything in multiple other clinical trials and the other nice thing so far right now is that once you get the CAR T, you don't get any other therapy. So, the average was about a year that patients were on no therapy after seven lines of therapy, where they felt better and everything was going well.

So, we're hoping that bringing that up sooner might make that longer. The other part is we have a lot to learn still. Everyone's T cells are different based on what we've been exposed to, what T cells we were born with. So, we're trying to figure all those things out to make the best -cells.

So, the allo part she was talking about is the trial we have hopefully opening soon where a lot of folks—we can't make CAR Ts necessarily for them because there are not enough of them because of the therapy we've had or for other reasons.

So, for those patients—or they can't wait four weeks to make them—so, if we have something that we can just pull, like a drug—we've actually found normal donors who seem to have what we want in T cells and made those already and we actually used genetics to knock out the things that can cause what's called graft-versus-host disease.

So, we don't want these cells to go in and say, "Wait, this is not my body. I'm gonna start attacking the liver or the skin." So, we can actually knock that out. It's a little bit science fiction, but it's really exciting that we can do that and then actually give these cells so that we don't have to worry about making them or potentially have to wait so long to give them.

Jack Aiello:
It is exciting. While folks might think average one year before you relapse, you have to again remember that these are patients that these are patients that have been heavily pre-treated, as you indicated, and what will happen when it moves further up in the treatment protocol.

Dr. Patel:
And we're looking at new antigens too and then combining antigens. So, how can we kill the myeloma so it doesn't get smart on us? It's really exciting.

Jack Aiello:
Dr. Lonial, anything to add on CAR-Ts?

Dr. Lonial:
No, I think that's a great description on the premise and the concept here. I think that BCMA, which is the target that most of the CAR-T cells are going after right now to me is the best target in myeloma because it's most narrowly expressed of anything else that we used, more narrowly expressed than CD38, which is the target for daratumamab, more narrowly exposed than CS1, which is the target for elotuzumab (Empliciti).

There are many different ways to get to BCMA. I think CAR-T cells are the ones that we are most optimistic and hopeful for if we can figure how to make those cells live longer. The longer the cells persist, the more likely you are to have disease control. In my guess, you probably need to be a little bit longer than six months to really have the optimal long-term outcome with CAR-T cells alone.

But the BiTE antibodies that were discussed earlier, that to me is another way to get to BCMA. That's looking very exciting and promising in early trials as well, as well as an antibody drug conjugate, which means you take the antibody targeting BCMA, but you put a piece of chemotherapy on the back of it. That selectively delivers chemotherapy to the myeloma cell. That we'll hopefully see some data on in the next few months as well, because that's another way to get to BCMA.

So, I don't think that one is mutually exclusive of the other. I suspect we're gonna use all of them, and we might use one as a bridge to get to another. I think these are all really exciting approaches that target that best antigen, which is BCMA.

Jack Aiello:
She mentioned BiTEs and ADCs, antibody drug conjugates. That was gonna be my next question to you. So, let me add on to that. The one other drug she mentioned was isatuximab, which is a daratumamab or Darzalex-like drug. My question would be an antibody, do we need another drug like that, and will that benefit patients?

Dr. Lonial:
I think right now, the trials that we've seen from isatuximab have been in different patient populations or different combinations than we've seen with daratumamab at least in the larger randomized setting. The pomalidomide-dexamethasone-isatuximab versus pomalidomide-dexamethasone trial is ongoing with daratumamab. So, I think really, does isatuximab add something different or unique? I don't know the answer to that.

I think having more than one option is always a good thing. I think from a patient perspective, if you've got two drugs fighting for even a similar market, that should drop the price. That's certainly an interesting way to think about it. I think there are reasons to want to have more than one option available.

Jack Aiello:
Staying with you, Dr. Lonial, a few questions came in—Michelle asked one that said, "Can BiTE therapies be done after CAR-T therapy fails?" Is there any reason to think it can't?

Dr. Lonial:
Yeah. There's no reason to think it can't. Loss of BCMA is something that has been reported with CAR-T cells, but at least in our patients that have relapsed, at least all of them have continued to express BCMA. The reason that the myeloma came back was that the T cells didn't persist long enough.

So, I can't tell you whether BiTEs will work afterwards because most of these trials say if you've had one BCMA-directed therapy, you can't have another one on a clinical trial. There's no reason to think why it wouldn't work because if the target is expressed, you should get activity. I don't know if you've had experience differently.

Dr. Patel:
Yeah. So, there are more trials now allowing because we've asked these questions. So, hopefully, we will have some answers in the next six months. We have had a couple of patients where one didn't work—let's say the BiTE didn't work and they went on to CAR T where it did work or vice versa. So, I think like we said, the antigen is there. It doesn't make sense that it wouldn't work.

I think the other thing is the other antigens that we have besides CS1, there are other new ones that we're coming up with. Early data, we don't results yet, but it's very promising that these antigens are also going to be just on myeloma and not on any major organs.

I think that's really important for us to find that as a scientific community so that we can use, let's say, a CAR T with BCMA, then maybe a BiTE with a different antigen, GPR5C, and then maybe AlloCAR T later if the T cells aren't working, if you haven't cured it by then. So, I think we have five years from now, even more options in terms of which order to put it in.

Jack Aiello:
So, Dr. Patel, let me generalize that question a little bit more—is there any therapy that once you've taken the CAR T and if you relapse—and this was actually asked by Cindy—is there any therapy after CAR T that somehow the CAR T would prevent or diminish the effects of using that newer therapy?

Dr. Patel:
Not that we know of. So far, we haven't. I think the other question is right now, we don't give anything with CAR T. In myeloma, doublets and triplets work better than single agents. The idea of these new cell mods and all those having better immune effects, can we combine that with CAR T to help with persistence of those CAR Ts?

Would daratumamab maybe help potentially or a CD38, because it does decrease regulatory cells? Will it help with persistence? I think it's more what can we add to it that's actually gonna make them better rather than precluding having a different treatment afterwards.

Dr. Lonial:
I think this has been done in lymphoma, where for instance, patients have relapsed after a CD19 CAR-T cell and been given drugs like pembrolizumab or checkpoint blockade and have re-responded. We've certainly anecdotally seen that as well as long as the T cells are persistent, the ability to turn them back on with drugs like pembro or drugs like the pomalidomide or lenalidomide that can reactivate immune function. There may be ways to wake those cells up.

Jack Aiello:
I read this morning that a couple of days ago, the FDA just approved or granted orphan drug status to the BCMA CAR T called CT053 and I think that's the China one that's LEGEND and has now been acquired and used by Janssen. I guess that just proves how far along and how quickly CAR Ts are really moving. So, it's exciting.

So, I'd like to invite Dr. Lin to join us because I keep wanting to find out what a hemapathologist does and so on. So, I'm inviting her up to the stage.

Dr. Lin:
Thank you for the invitation. So, I'm a pathologist specializing in hematological diseases, which means that I make diagnoses on diseases such as leukemia, lymphoma, or myeloma. When I start off my first career in University of Arkansas in 2000, we had seen a lot of myeloma patients.

Some of you come from Arkansas, Little Rock. Dr. Bartleby was treating patients with thalidomide. As you have heard from Dr. Patel and Dr. Lonial, myeloma drugs have grown so many more now over the years exponentially. So, now, you have so many choices.

So, for that, as pathologists, we work primarily behind the scenes. We contribute in several different ways. First of all, when our clinicians suspect there's a myeloma, we usually get a biopsy to read, these bone marrow biopsies usually include aspirate smears and the core biopsies.

We estimate the tumor load. As you heard from Dr. Patel, estimating the percentage of plasma cells in the bone marrow is very important in terms of determining whether our patients have high risk of smoldering myeloma or myeloma, so, 60 percent versus 50 percent or 10 percent makes a difference. We estimate the tumor load. We also assess the cells morphology to assess whether they are more immature, how abnormal, how deviated are they from the normal plasma cells.

Beyond that, we also look at some other things, look at biologies so we can see that I do. I look behind the microscope, not only at the cellular level, but also at the genetic and molecular levels to identify high-risk factors. One of the tests that we do is called a FISH in cytogenetics. We look for deletion of p53, which is usually considered to be adverse factors, those biomarkers for aggressive disease.

Jack Aiello:
So, can you say a little bit more about that p53 thing? I hear about deletion 17. I hear about deletion 17p. I hear about p53. How are they related?

Dr. Lin:
Okay. So, the gene is called a TP53. It's located on chromosome 17p. So, we can look at it in different ways. One way is to look at the chromosomes, like as I show here. So, I look at chromosomes. Sometimes, that is not sensitive enough. So, you also do FISH, which specifically targets that particular gene.

So, the issue with FISH is that it's more sensitive, but it only looks at the particular gene. If we look at the whole chromosome, the karyotype, we can tell more than just the p53 deletion, but the other adverse factors, such as 4;14 translocations, so on and so forth.

So, there are also many other ways we can contribute as pathologists. So, we can look for the biomarkers from the immunohistochemistry, like looking for p53 expressions at the protein level. So, when there's a mutational deletion, there tends to be expression of that particular protein.

Also, we can look at the gene expression profiling as well as the next generation sequencing to see if there's any mutation. If you have mutation and deletion of p53, that tends to be more aggressive than just a single isolated deletion or mutation.

Dr. Lonial:
So, I think that's a really important point, the idea that p53 is a gene which is responsible for DNA repair. It's located on 17p. For the trivia night that you guys go to, the p in 17p stands for petite, because it's the short arm and the long arm is q because q is after p. That's actually where that came from.

Dr. Lin:
Right.

Dr. Lonial:
You can have missing portions of 17 where you don't have a copy of p53, but you've still got one functional copy of p53, because you have two copies of every gene. If you have a mutation, that's a much bigger deal, because you may or may not have a normal copy if one is missing, and the other is mutated. That's a subset that we know early on does not respond nicely to therapy or if they respond, they don't stay in remission for very long.

Jack Aiello:
So, if a doctor tells me you're a high risk because you have deletion 17p, does that mean all my myeloma cells have this deleted chromosome? Does that mean a certain percentage do?

Dr. Lin:
That's a very good question. When we do FISH, we can actually quantify how many cells, because we normally will study 200, sometimes even 500 cells to see what percentage of cells actually have the deletion.

Depending on the clinical data using different kinds of testing assays, some use the 50 percent cutoff, others use lower cutoff. I'll ask Dr. Patel and Dr. Lonial to answer that question. But the idea is that the higher the percentage, the more aggressive it's likely that the tumor may not respond to therapy. So, that's a very good question.

Jack Aiello:
Do you all, Dr. Patel, use a standard cutoff?

Dr. Patel:
So, we use basically anything that's positive per our FISH assays we consider positive. However, the more cells that have 17p, I keep a closer eye on it. The French data shows that if you have 60 percent, that's really where it's positive, but we also have data that even if it's lower—and everybody has their own sort of positive, so, it's hard to compare all these trials.

But for me, if it hits positive and my pathologist is telling me it's positive, then it's not just a false negative, then I consider that as positive.

Jack Aiello:
So, positive could be 1 percent of the cells, yes, no?

Dr. Lin:
That's a very good question. The way we do the test, in many places, we enrich the sample, meaning we only test the samples that have been selected over plasma cells. So, then we can tell you exactly what percentage of plasma cells instead of percentage of all the cells that we have to look at that has the deletion. It's a very important question to answer to ask.

So, that's why sometimes when you read the pathology report, it's very complicated. It can be quite intimidating, because you have to look at what you're reading. I have a friend whose wife was diagnosed with myeloma. And in the beginning, she

was told that you have only two years of survival, because you have this deletion. It turns out it was not exactly the case. The family was very devastated.

So, even for sometimes physicians, it can be quite intimidating, let alone for the patients sometimes to read these complicated reports. The question here you asked is very important—what percentage of the tumor cells actually have the deletion? That is the key question.

Dr. Lonial:
I think the 60 percent cutoff is what you need if your readout is a short-term readout, meaning within three years, to see whether there's a difference. At least in our view, 17p is sort of like being pregnant. Either you have it or you don't. If you have it but it's at 20 percent or 30 percent, it's still there.

With subsequent relapses, it's gonna get enriched in higher numbers. So, it's somebody that we're much more aggressive with in our early therapy to try and prevent the sort of emergence of drug resistance than somebody who doesn't have it at all.

Jack Aiello:
That might also explain why at diagnosis, maybe nobody mentions anything about 17p, but at relapse, someone says all of a sudden you're 17p, a small percentage was there initially. Unfortunately, as the clone changes, that percentage has increased.

Dr. Lin:
That's a very good point.

Dr. Lonial:
Or you acquired it. We know that, as you said, myeloma cells get smarter as they are around longer. If you are a cell, one of the things you'd want to do is get rid of p53, because it allows you to genetically do whatever you want. So, as a cell evolves, it may lose one copy of 17p as part of that evolution.

Dr. Lin:
That's a very good question.

Jack Aiello:
So, let's talk a little bit about—it came up earlier, MRD, which is minimal or sometimes measurable residual disease. First of all, Dr. Lin, you test for MRD, and how do you test for MRD?

Dr. Lin:
Sure. Yeah. So, there are two ways to test for MRDs. What we do is called flow cytometry. We look at millions of cells, a minimum of 2 million, sometimes 5 million. Some people even do 10 million to look for those abnormal cells. We get to the sensitive in the 10^5. So, it's a very sensitive test.

There's another way to test for MRDs, which is you can do the next generation sequencing to specifically look for the sequence studies unique to this particular myeloma. So, that's also very sensitive. I just wanted to add one more thing that we do for the conditions, which is that Dr. Patel mentioned about BCMA.

We also can test for that, which is the therapeutic targets that we sometimes do. So, regarding the MRD, as I said, there are two ways to do that. We routinely do that in our hospital whenever patients get treated and we do those for our conditions and hopefully, they will inform the therapy.

Jack Aiello:
So, that's kind of my next question. But just for comparison purposes regarding sensitivity, you indicated that MRD testing via those two methods is either 105 or 106 sometimes sensitivity levels. How does that compare with a normal SPEP blood test that I'm taking to look at my M spike and such? How sensitive are those tests?

Dr. Lin:
It would be far more sensitive. I should say there are many ways to do MRDs. If we test the bone marrow, it's a snapshot, right? You take one sample from one location.

So, there are ways you can actually test for the proof of blood to see because now, there are more—we have not been doing that but there are ways to test for the circulating tumor DNAs or some other things that you can actually get a global view ideally that maybe this is coming from bone marrow in one location but if there are any other focal lesions in the part of the body where you can actually test it.

So, I'm sure Dr. Patel and Dr. Lonial know about all these testing de-circulating DNA and circulating other markers that could tell us whether there's minimal residual disease. As far as the meaning of the MRD, how that's gonna guide the therapy, I'm also gonna defer to these experts to talk about it.

Dr. Lonial:
So, if you just think about raw numbers because that's probably the easiest way to think about it—MRD by next-generation sequencing is basically one in a million is what you're detecting. By flow at 105, it's 1 in 100,000. By routine SPEP, it's somewhere around 1 in 1,000. So, it really is significantly more accurate. The question is how does that really impact therapy.

Jack Aiello:
I'm gonna get to that, but MRD is new to a lot of us. There is a two-minute video on MRD that we cue up. Can we run that to bring everybody up to the same level?

Video Speaker:
MRD is the term used for the small number of cancer cells that remain in the body during or after treatment. Monitoring MRD can provide detailed insights into a patient's disease status and their response to treatment. The presence of MRD in a patient's body may be associated with increased likelihood for the disease to return after treatment.

MRD is usually tested for in the blood or bone marrow. MRD is currently detected using the following techniques—flow cytometry, polymerase chain reaction, next-generation sequencing, and next-generation flow cytometry.

An MRD-positive result means that residual disease was detected. An MRD-negative result means that residual disease was not detected, also known as undetectable MRD. MRD-negative results indicate that a patient is less likely to relapse. MRD results assess the depth of response to treatment, assist in evaluating whether a treatment is working, monitors remission status, and aids in early detection of relapse.

Questions to ask your healthcare team about MRD testing—do I need to have an MRD test? When and how often should I have an MRD test? What does an MRD-positive or MRD-negative status mean for me? How might MRD results affect my treatment plan? What tests are available and how do they vary in sensitivity and accuracy? Is MRD testing covered by insurance? Is financial assistance available?

Jack Aiello:
Let's start at the beginning. Dr. Patel, what tests do you order for that newly diagnosed myeloma patient? And in particular, does it include MRD testing?

Dr. Patel:
Sure. So, for us, a lot of my patients come from the outside center where they've had some studies done, and we usually just try to make sure everybody does the blood work, so SPEP and immunoglobulin light chains. We make sure they've had some type of imaging, either PET scan or MRI, which we'll talk about a little bit later.

In terms of bone marrow, you have to have bone marrow for diagnosis. I've had a couple of patients come to me having started treatment and never had a bone marrow. That doesn't happen very often, but that's really important. That's where we get all this genetic testing information from from the beginning.

We don't do MRD testing at the beginning. When you're newly diagnosed, we have lots of cells. The idea of what MRD is are there any cells left after we've started treatment? So, we do FISH testing, and we do cytogenetics and all those things that Dr. Lin talked about to help decide are there high-risk features, or are there standard risk features? That helps us tailor our treatment a little bit. So, no MRD testing at the beginning. We usually do it after treatment.

Jack Aiello:
Do you do it then—when you say after treatment, when a patient relapses?

Dr. Patel:
Usually, we do it after—let's say someone's newly diagnosed and they've gone through transplant, usually three or six months depending on the center, we do another bone marrow to see the response. That's when we do MRD testing.

Usually, that's also when the M-protein has gone down to possibly zero. That's usually when you can't find the myeloma cells just by looking under the microscope with stains, which is called IHC. That's where we really want to know how deep, if we can go deeper, can we really not see that myeloma?

Jack Aiello:
So, in that case, the patient is—chances are, they're in a complete response?

Dr. Patel:
Potentially.

Jack Aiello:
And then you look at MRD…

Dr. Patel:
…to see if they're MRD-negative on top of it.

Jack Aiello:
Via flow.

Dr. Patel:
For us, we do via flow. We are working on the next-generation sequencing, as that is approved to do that as well.

Jack Aiello:
And next-generation sequencing might change that, because they'll want you to do an NGS test at diagnosis, right?

Dr. Patel:
Right. So, at that point, you want to know how to find those cells. So, to have something at baseline is important.

Jack Aiello:
Okay. Dr. Lonial, we hear lots about MRD in terms of determining how much myeloma is in the body as a more sensitive way of checking things out compared with blood tests, but can you talk about MRD? Do you use it regularly? Do you use it to help guide any kind of treatment decisions? For that matter, should patients be requesting MRD testing if they're not getting it?

Dr. Lonial:
That's a tricky question.

Jack Aiello:
I know.

Dr. Lonial:
I will tell you at our center, we do MRD testing and we collect the data to really pair it with longitudinal follow-up to understand where MRD testing can be most useful. I think there's no question that patients that are MRD-negative have a better long-term outcome than patients that are not MRD-negative.

What we don't know is whether you take somebody who's MRD-positive and change their therapy to make them MRD-negative, do you actually change their outcome? You might say it's only logical that you would. The reality is in many diseases, that is not the case, because MRD testing really reflects what we call prognostic indications as opposed to predictive, meaning if you change it, you can actually change the outcome.

Those studies are currently ongoing now. One of the cautions—like I said, we collect the information on a lot of patients at different time points, as Dr. Patel indicated, but one of the concerns that I have when I think about using MRD negativity is one of my European colleagues will routinely get up at meetings and say if you're high-risk and you're MRD-positive at one year, you won't be alive in two years. I've got an entire clinic full of people that will prove him wrong.

The reason why our clinics are different from the clinics of this colleague in Europe is that we use three-drug continuous maintenance in our high-risk patients. And even if you're MRD-positive, you can control the clone a much better way than you can if you have limited access, because you can't give three-drug continuous maintenance, and you have to stop treatment in one year.

So, understanding what are the limitations of the data that's out there telling us MRD is the answer is something that I think is a subtle point here. We may get to that point where MRD can drive decision-making. At least right now, I don't feel like I have enough data to use it that way. I don't know how you…

Dr. Patel:
…same. We do it and it helps me guide prognostic discussions, but in terms of predictive, where I can stop maintenance, that's another question I discuss with my patients. If you've done two years of maintenance where in Europe, everyone stops, in the US, we try to keep going.

Could that help us in the future decide if we can stop maintenance? That's the exact clinical trials we're waiting for, because we don't want to undertreat folks that are high-risk, but we also don't want to overtreat folks that are standard risk.

Dr. Lonial:
And I think it's important to realize in the CAR-T cell trials that you discussed, there are many patients who are MRD-negative at day 30 and are relapsing at day 90. So, MRD-negative is a path towards getting to elimination of the clone, but just because you achieve it doesn't mean you can stop, or you're cured.

Dr. Lin:
Sometimes I hear from our clinical colleagues tell me that I have this patient who has MRD and has been living in complete remission. From a pathologist's point of view, I look at the smears, and I can actually sometimes say that there's a difference between patients who have MRD who relapse than who don't relapse.

Many of those patients who have MRD that didn't relapse, their myeloma cells don't look so ugly. They don't look so immature and so deviated from normal. They tend to look more or less like the mature plasma cells that we see. They're sort of like the ones you see in like the MGUS or smoldering myeloma.

So, in that sense, I think assessing the morphology and other biomarkers like the adverse cytogenetics or FISH probably are more important than just the MRD itself in determining who is likely to relapse or not.

Jack Aiello:
One of the trials that just opened up is out there by SWOG, one of the cancer research organizations. It's trying to ask the question of MRD negativity and can we use it to affect treatment. And in particular, in maintenance, it's asking the question

if you are MRD-negative at the start of maintenance and then two years later, can you stop treatment or not? It's randomizing those patients into stopping treatment.

I think it will be awfully important, but it's also a long way down the road before we have results of that trial. Honestly, patients, if they know they can stop treatment, that's a good thing. As doctors too, I'm sure you can say we can stop for now. So, it's an exciting area.

So, what about the question about should patients be asking to get MRD testing? Dr. Lonial, I'm not sure you answered. So, I'll turn it over to Dr. Patel.

Dr. Patel:
I do. I think MRD—any extra information you can get, especially because myeloma is something that's a long-term treatment. So, if I have MRD testing now, two years from now, I want to know that things are changing. The MRD might be a predictive test by then with all the trials that are ongoing.

So, in myeloma, this is what I tell my patients all the time—my goal is to give you the longest PFS that we can so that we have new therapies, we have new technology, and we have new information I can use from your previous treatments and your previous information that I had to then make the right decision at that point.

The more information we have from when you first start or even in first relapse, it's gonna give me more information in the future to really know what to do with it, because we'll have learned so much more. So, I think this is the first real biomarker in myeloma. We have other things that we're looking at like 11;14 and things like that that we're starting to get more and more biomarkers—BCMA. But MRD is actually the one we've had the longest that is going somewhere and that we're testing further.

Dr. Lonial:
By the same token, having measurable disease by SPEP, sort of old school technology, doesn't necessarily mean that you have to intervene either. So, I agree that you want more information. If somebody goes from 200 to 1,000 in their standard risk by MRD, I don't know that I'm necessarily gonna intervene with therapy, just as if somebody goes from 0.2 in their SPEP to 0.5 in a year. I don't know that I'm gonna intervene on that patient either.

So, I think there's a learning curve, and data is helpful to figure out how to use that, but it shouldn't be an, "Oh my gosh, there's something there. Now I've got to do something."

Jack Aiello:
I haven't mentioned it. I'm not sure it's on the slides. But those answers indicate why it's so important to get a myeloma specialist on your team, why it's so important to get second opinions from them, so they can work with your community oncologists and such. Because it really is such an individual thing to assess how a given patient is doing rather than kind of following some flowchart of treatment paradigms.

Dr. Lonial, I hear about gene expression profiling, and I don't exactly know what it is. Is it used these days? What do you do with it? Is it used outside of clinical trials? Can you say a little bit more about it?

Dr. Lonial:
The gene expression profiling is something actually that was brought to us by our colleagues at Arkansas years ago as a way to sort of be better than just FISH. FISH tells you where you are now, but it doesn't tell you how functional or lack of function those many genes and proteins are. So, gene expression profiling is another way to do that.

There are a couple of commercial tests, maybe down to one now, that can do that. It's not a test we routinely use. But I think it's gonna end up being replaced with RNA sequencing where you get both molecular data, and you get the expression data as well. Even that, right now, it's unclear what that mutational data can really tell you, because unlike other cancers where you have an EGFR mutation, and you use drug X, we don't know that in myeloma yet.

The trial to really answer that question of can a mutation tell you what treatment to do actually just opened last month, and it's called MyDRUG, and that's a trial where patients with early relapse get sequenced as part of the initial therapy, and then their treatment is defined by what mutations they have. And then if they don't have any, they go on something different. That's the first trial to really answer that.

Jack Aiello:
I want to move on to imaging. If you actually look at the definition of MRD, you mentioned the two possible tests, but it also includes the fact that you should have imaging down by PET scan or PET CT or MRI and a lot of us start off with X-rays. So, Dr. Patel, can you talk more about imaging and what patients should be getting or not getting in the case of some of these imaging tests?

Dr. Patel:
Sure. So, I think at diagnosis, everybody should have imaging of some sort. I believe, and I think most people would believe, that skeletal surveys are probably not the best way. So, for us, we either do a PET scan to look for the metabolic reaction of these cells, so we can see if it's really hot and does it go down, does it go away completely versus MRIs?

The standard is MRIs of the spine, but now, we have whole body MRIs. Actually, at MD Anderson, we just got whole body MRIs a few months ago. It looks like the bone is a little bit better. There are certain questions. They don't do the same exact thing, but they are much more sensitive than just skeletal surveys, number one. Most of the time, right now, we're still learning a lot of data on which one we do, but they're both options.
It helps if you don't have any bone disease, technically, we don't need to keep getting them every few months or even regularly in my opinion. We need them, especially if you have new pain or anything that seems concerning, but if you have bone disease, then it helps us follow that bone disease throughout your treatment.

So, initially, for MRD, yes, we want the bone marrow to go away. We want the SPEP and the blood test and the urine test. We also want to make sure that if there was one extramedullary disease, meaning its's outside of the bone or the bone marrow, if it's in the lung or the liver, we want to make sure that went away.

Then we also want to make sure the bone lesions are better, especially if there was one that could potentially cause fracture in the future or anything like that. As we treat, the idea is that we get these bone lesions stronger.

There are points where they're still weak and if we need to do a nailing or something like that to help support, it sort of helps all of those things for prognostic, once again, but also, for quality of life to make sure we don't miss something that's changing.

Jack Aiello:
Okay. Dr. Lonial, kind of the same?

Dr. Lonial:
I agree. I think the International Myeloma Working Group just published their new guidelines on imaging and myeloma. They've actually removed skeletal survey from that list now. The lowest level of imaging that's sort of acceptable, if you will, is low-dose whole body CT scan, which does let you get a sense for the bones.

There is this controversy about MRI versus PET/CT. What I like about PET/CTs is it doesn't necessarily—it helps me to differentiate old versus new disease a little bit better than I think an MRI does. I think that's a debate that's ongoing.

Jack Aiello:
So, let's follow up with that PET/CT, which apparently looks at some sugar uptake. As a result, I hear patients saying, "Well, I've decided to eliminate sugar from my diet, because obviously sugar causes cancer." Can one or both of you address that comment?

Dr. Lonial:
There's no data that speaks to that in myeloma. If you eliminate—to me, it becomes a quality of life issue. If you can—I had a patient whose wife wouldn't let him have chocolate chip cookies, and that was like the one thing that made him happy. Eat the chocolate chip cookies. Forget that. Sugar is a life leader, a life important piece for every cell in your body.

If you cut out sugar from your diet, your body is gonna get sugar from someplace else if there's active myeloma. So, the best way to address it is not to say we're gonna cut off the food supply, it's to say we're gonna cut off the tumor. That's really the way to get rid of it. I'm not aware of any data about glucose limitation improving outcomes in patients with myeloma.

Dr. Patel:
I think a lot of my patients ask me about keto diet, because that's a big thing right now. It's more that you make sure you have a healthy diet. I don't want you to have a heart attack or your kidneys have too much protein and now, they're not working, and I can't give chemo. So, usually, newly diagnosed patients I say eat what you're eating. We'll slowly work on nutrition after transplant, three to six months. Then we talk about a heart-healthy diet in general.

Eliminating sugar is important, because I don't want you to get diabetes when we gave you all these steroids. So, long-term, but short-term, I don't think that—I don't think sugar causes cancer. It's more everything else that can do long term that we want to make sure we bring back down too.

Jack Aiello:
Related to bone disease, we haven't talked about it yet, but what about these bisphosphonates? You have pamidronic acid (Aredia) and zoledronic acid (Zometa) that we know of. You have denosumab (Xgeva), which is relatively new. So, Dr. Patel, can you talk about the usage of bisphosphonates?

Dr. Patel:
Sure. We know that even in smoldering patients, this came up recently, but even in smoldering patients, if they have bone loss of any kind, we know that bisphosphonates actually does help protect bones. Then there are some changes it can do the immune system that it actually helps.

So, it's really, really important, especially if you have bone disease, that we have some type of bone-strengthening medicine to help. It's not something, "Oh, I gave you a dose, and your bones are perfectly normal in a couple weeks," but over time, it does help strengthen your bones a lot faster.

In terms of Zometa versus Xgeva, we don't know. We have both options, which is great.

Jack Aiello:
Xgeva is the other name for denosumab.

Dr. Patel:
Denosumab, sorry. So, denosumab versus Zometa, we have a lot more data with Zometa. Denosumab could be more expensive for some of my patients if the insurance doesn't approve it. So, some of those things come into play. My dentists love denosumab, because the half-life is 30 days. So, if someone needs something in the future with your teeth, they think that it decreases the risk, but in the end, we pick whichever one makes the most sense.

But there's a trial that was done head to head but a lot of issues to say one is better than the other. It was made to say that they're both equivalent to make sure you don't get factors and things like that from myeloma.

Jack Aiello:
Dr. Lin, you heard earlier that X-rays have been discouraged, if you will, as a way of diagnosing myeloma. Do you agree with that? Do you look at those tests and kind of say…

Dr. Lin:
…X-rays. I'm gonna have to defer that to Dr. Lonial. I usually don't—I look at the clinical history and things and check for evidence of a disease to support the diagnosis of myeloma. I usually read my specimens, the bone marrow specimens in the

context of clinical pictures, because there are so many things that can cause the bone changes. Prostate cancer is one of them that can cause lesions or hormone changes.

Jack Aiello:
Talk into this space a little more.

Dr. Lin:
Sorry. I always take into consider the overall clinical findings.

Jack Aiello:
Other comments on bone disease that patients should know or ask about? Have we covered that area?

Dr. Lonial:
I think it's important that patients take calcium and vitamin D supplementation, particularly if they're on denosumab. That's a really big deal. Zometa may give you some level of hypocalcemia, but with denosumab, it's much, much lower. So, I think making sure you're on some sort of calcium supplementation is important.

Jack Aiello:
Why would you recommend denosumab over Xgeva? I'm sorry, over Aredia or Zometa?

Dr. Lonial:
If somebody's got renal dysfunction, I think that's an easy one. At least in our hands, if people develop bone disease in the context of being on zoledronic acid, that in my mind is a reason to think about switching, because it's a different mechanism, but that's me.

Dr. Patel:
I have some patients who have side effects from the infusions. So, then if we try to switch over and see if the subcu injection, they have less side effects. But vice versa, I've had a couple of patients with denosumab get really bad skin rash. It's very rare, but then we switch to the other one. So, it's sort of patient-specific.

Jack Aiello:
How long do you recommend someone be on bisphosphonates?

Dr. Patel:
So, I guess it depends on when. If it's early and newly diagnosed, we usually do Zometa for two years. Denosumab in the trials continues forever. We have trials, and then we have actual life. So, most of my patients after two years, we stop unless there's a lot of bone disease, and then we try to keep going. In relapsed/refractory, we try to just keep going, especially if there are new bone lesions. It's depends on where we are in the stage of myeloma.

Jack Aiello:
And Dr. Lonial, kind of the same?

Dr. Lonial:
Yeah. One year, we go to every three months and we tend to go a little bit longer than two years, but there's no hard data one way or the other.

Jack Aiello:
Right. You're really trying to avoid the osteonecrosis of the jaw and the negative effects that it can have.

Dr. Lonial:
It's still a pretty low number.

Jack Aiello:
There was a question that came in that said for patients that cannot bisphosphonates, are there other bone-building therapies out there? We've talked about denosumab or Xgeva. Is there anything else?

Dr. Patel:
Not that I know of. This is where we say let's make sure your vitamin D, your calcium, all of that is up to par. If we can do bone-strengthening exercises, but that completely depends on where the bone lesions are how much we really—I have my patients see our orthopedics docs.

If there are certain lesions that I don't want to cause fractures or things like that, we come up with a plan of what's okay. Swimming is okay and walking is okay, but not weightlifting, things like that. We sort of have a team approach of giving patients what type of bone strengthening exercises are the best for them.

Jack Aiello:
That's a good question. We do get patients asking, "What type of exercise should I be getting or limits should I put on myself?" "I'm a jogger, is it still okay to jog?" "I lift weights, what about that?" What do you tell them, Dr. Patel?

Dr. Patel:
It's very specific. So, if I have a patient that has a lesion in the arm and we adjusted radiation and we've treated it but it's gonna take months to heal, this is where I have my orthopedic doctors help me to decide when is it okay that now I can do maybe five-pound weights, versus if you have just lytic lesions that aren't at risk for fracture, then it makes sense that we don't have as many limitations.

But if you have a vertebral fracture or a lesion that looks not so stable, then we try to make sure that's stable first. That's where I use my bone doctors to help me make that plan for them.

Jack Aiello:
Many patients are diagnosed initially, because they've got vertebrae compressions. Do you still recommend these days that patients look at kyphoplasty or vertebroplasty as a treatment for repairing that compression? Dr. Lonial?

Dr. Lonial:
Yeah. I think in terms of pain control, it's really quite remarkable how much relief patients can get. That to me is the main indication for using those technologies. You do get some bone height back. That's to me not the main driver. It's really pain control that's the main driver. I do think—I think just like we talked about a balanced diet, I think the more you do, the more you can do.

Our goal in therapy is to get you back to the same life expectancy that you would have if myeloma had never bothered you. So, that means you have to go back and do the things you were gonna do if you wanted to live longer than you currently are.

So, that involves physical activity, health maintenance visits to the primary care physician, all those kinds of things need to come back in the mix to live a long healthy life.

Jack Aiello:
I want to go back to my favorite thing of bone marrow biopsies. We hear that the results of a bone marrow biopsy, which are used to determine the percent of plasma cells in there and so many other things, the FISH and cytogenetics test and now the MRD testing, the results of a bone marrow biopsy are very dependent on where that sample is taken.

So, is there anything that can be done to overcome that randomness, or is it something that we patients overthink or overworry about and we shouldn't be concerned with that? Dr. Patel?

Dr. Patel:
Yes. Myeloma is very patchy. That's what I was taught when I was a fellow. I do see that. I think in general, when we do bone marrow biopsies, we get the information we need. There are specific cases where something just doesn't fit.

So, for instance, if I have a patient who we thought was smoldering and we get a biopsy and it shows 10 percent myeloma in that biopsy report but their hemoglobin is low, lower than I would expect and there's no other cause for it and their

myeloma proteins are really high in the blood, then I might repeat it and say, "Wait, this just doesn't fit." But if the clinical situation fits, the likelihood is it's the right thing.

Now, can we fix that or is there a way to get more information on the whole bone marrow? That's where whole body MRIs might help us in the future. There are trials looking at scores and different ways to look at the entire bone marrow on an MRI and seeing if those changes could correlate with what myeloma is doing.

So, sometimes I will get a PET scan or an MRI to look more specifically for lesions throughout the bone marrow to really say, "Is that 10 percent really what's going on?" Or is it that mostly 60 percent and that one spot is 10 percent? There are other imaging tools sometimes we use as well.

Jack Aiello:
Dr. Lonial, I hear something about mass spectrometry tests that are going on, predominately at Mayo and maybe that's moving forward. Is it? What are the benefits of mass spec when that becomes available?

Dr. Lonial:
Yeah. I think mass spec is just a more sensitive way to look for the protein. The nice parts about mass spec really are more on the pathology side in the sense that it reduces the staff that you need in the lab to be able to run all these SPEPs. So, currently, at least in our lab, we have three or four people that run SPEPs constantly, because they're always coming in. You can reduce that to one by doing mass spec.

Mass spec also gives you more sensitivity than an SPEP. So, you may be able to get down to 10-4, 10-5 in terms of sensitivity. And it allows you to discriminate between dara in the blood and the original n-protein that's in the blood, which right now is a little bit more challenging with routine serum protein electrophoresis.

It can be done in experienced labs. Even some patients whose antibody may look like dara, it becomes a little bit more challenging. Mass spec can very clearly delineate those. It is a test that I think is coming. It's not gonna replace a bone marrow. It will probably replace SPEPs. We're probably gonna be up with them the next month or so.

Jack Aiello:
So, you bring up a really good point with respect to daratumamab or Darzalex in that it might affect a normal SPEP reading for your IgG number or your M spike a little bit. So, what has to be done in that case? Is it the hemapathologist that has to read things differently? Is it a different test that has to be done? How does that work?

Dr. Lonial:
So, there is a test you can do. It's called the dara test, which basically pulls dara out and then runs the SPEP and allows you to look at is the original protein there or not. In most patients' case, our immunology lab can differentiate dara and they'll say the original protein is gone but there's a small dara peak there that's about 0.2 or 0.3. That's usually enough for me. If they can clearly distinguish it, then I'm okay with it. But you can do this anti-dara test if you want to try and eliminate it.

Jack Aiello:
Does MD Anderson, Dr. Patel, use this or Dr. Lin, use this dara test?

Dr. Lin:
I'm not aware of it.

Dr. Patel:
We don't usually use it. I can ask for it if there's a specific question that I need that information for. Then we can get it done, but it's not something we routinely do, because a lot of my patients are on dara. It already takes us a little bit of time to get the SPEPs back to add another test to it, because it does take extra people to do this. We ask for it specifically if there's a question that it would affect.

Jack Aiello:
I had one person ask if dara actually affects the lambda level. Does it?

Dr. Lin:
Actually, when we do the bone marrow study by flow cytometry, we can actually find that very early precursor of the B cells can look like monoclonal because, actually, the dara is the kappa, make it look like a kappa, but it's actually an artifact.

Dr. Lonial:
We did look. It does interfere with the SPEP, but the free light chain assay is not affected by dara. So, it shouldn't have an impact there.