Andrew Schorr: Hello, I'm Andrew Schorr. Welcome to this Patient Power Roundtable discussion about multiple myeloma. And we do this each year, during the American Society of Hematology meeting where experts come, or this year virtually, from around the world to discuss the latest in blood-related conditions, and certainly, blood-related cancers and myeloma always has, thank goodness, a lot of discussion and real progress.

This program is supported financially by GlaxoSmithKline but like all our programs, they have no editorial control. I want to welcome our experts who are joining us today. And that is Dr. James Berenson from Los Angeles, Dr. Robert Orlowski from Houston, and Dr. Rafael Fonseca from the Phoenix area, Scottsdale, Arizona. And I want to have them give you their titles so you really understand these are real top experts and myeloma subspecialists, who also have been presenting research each year at this meeting. Dr. Berenson, what's your title there in Los Angeles?

Dr. Berenson: I'm Medical and Scientific Director at the Institute for Myeloma and Bone Cancer Research and been working in myeloma about four decades now, both clinically and preclinically and even epidemiologically.

Andrew Schorr: Right. Dr. Orlowski, how about you? What's your title at MD Anderson in Houston?

Dr. Orlowski: I'm the Director of the myeloma section here. And so I have oversight over clinical research as well as laboratory-based research. And we try to have a nice flow between the bench and the bedside to improve patient outcomes.

Andrew Schorr: And Dr. Fonseca, how about you at the Mayo Clinic?

Dr. Fonseca: Thank you again for the invitation. First and foremost, a myeloma doctor. But I also serve at Mayo Clinic as the Interim Executive Director for the Mayo Clinic Cancer Center.

Andrew Schorr: Okay. And how long have you been in the myeloma field?

Dr. Fonseca: I've been doing this for about 25 years now too as well. So not quite as much experience as Dr. Berenson but trying to build on that.

Andrew Schorr: Okay. All right. Let's begin. First of all, let's just go around, Dr. Berenson, is the ASH meeting important this year? Has there been continued progress and interesting discussions that can really be positive in the treatment of patients?

Dr. Berenson: Yeah, I mean, it's an important meeting, unfortunately, this year, the most important part of the meeting is interacting with colleagues like the two of these guys and trying to [inaudible] new studies, and obviously, that's wanting. So that's frustrating for me, as a guy who wants to move the field forward. But we're trying to do with it the best we can.

Andrew Schorr: Right. But do you think that there is maybe even more hope for patients now living longer and living better? When patients come to see you, they're saying, "I've got this diagnosis. Oh, my God." Is it a hopeful message that continues?

Dr. Berenson: Oh, yeah. People are living so much longer. I started doing this 40 years ago, and it was 25 months. And now we're well over a decade in our clinics. So, it's a lot different. Still not curing most people. But certainly, it's a lot different than it was when I started.

Andrew Schorr: Dr. Orlowski, how about you? Are there certain headlines that strike you from the research being presented, that could be, I don't know if you'd say transformative, but really showing very positive evolution of myeloma care?

Dr. Orlowski: I think the exciting aspect about myeloma is not only have over the past 10 to 15 years, there have been a multitude of new drugs and mechanisms of action developed. But if anything, the pipeline of new agents is even larger. I think for me, the exciting things at this ASH are some of the immunotherapies that go beyond just B-cell maturation antigen or BCMA. And we're starting to see data about the efficacy of immunotherapies targeting other cell surface proteins including GPRC5D and FCRH5, for example.

And I think that gets me excited at least because as with chemotherapy, where one drug was okay, but when we combine them, the combinations were much better. I think we have the same hope for immunotherapies, that if we combine immunotherapies against a couple of different targets, that it should be even more efficacious. And the numbers that we're seeing in terms of response rates now are better than we've ever seen, even though the patients have had more and better therapies, which means that theoretically, the myeloma should be less sensitive. So I think there's incredible hope for the future.

Andrew Schorr: Dr. Fonseca, so it gets really complicated now as to which patient should have which drug or be in a trial when? So how do you sort that out for people? How do you figure all this out?

Dr. Fonseca: Well, I hold a philosophy that we should always offer to our patients the best there is upfront, when you have that available, and we have done that historically, with our combinations for frontline therapy. We've introduced as part of that in many of the regimens transplant, but as we see, the players that we have that are out there in the periphery that are being tested in relapse or refractory setting, the obvious question is how fast can those move towards the front line?

So, you heard from Dr. Orlowski, for instance, that immune approaches are really one of the key aspects of this ASH meeting. And the question could be, could they be use from the get-go, could they be replacing transplant? Could they be cleaning up after transplant? If there's anyone that is MRD positive? Could they be using combination from the get-go?

There's this year a phenomenal study published in the *New England Journal* that looked at such an approach for acute lymphoblastic leukemia. Now, why not do it in myeloma? So I think this story is just getting started. And with what we're seeing, I think there's significant room for optimism for patients.

Andrew Schorr: So Dr. Berenson, some patients have heard this acronym MRD, minimal residual disease, and that testing is being used. Not everybody agrees it's significant or do you do anything different? What's your view about MRD testing?

Dr. Berenson: Well, I think that the key to a test is what do you do with the information, not just I'm going to pat my patient on the back and say, "You're MRD negative, therefore, you will live longer or shorter." I think if you're going to do a test, I'd like to see us be positioned to act on it. And I think MRD is wanting. We don't have data to suggest what to do with the information at this point. Those studies really haven't been done, they should be done, they're long term studies, obviously, given how long myeloma patients are living, but I think they're important.

I think also limitations of that, of course, are the heterogeneity of involvement in the marrow. Patients who, for example, have disease, even outside the marrow may be MRD negative, they're certainly not doing well. So I think there are some limitations here that need to be considered before we move this into regular clinical practice.

Andrew Schorr: Dr. Orlowski, do you agree? I know there's some debate about MRD testing.

Dr. Berenson: I agree. But I think the good news is that there are as Dr. Berenson mentioned studies underway, I'll give you one example which is an ongoing SWOG study that we're leading, which is looking at lenalidomide (Revlimid) versus lenalidomide plus daratumumab (Darzalex) for maintenance after transplant. And then at two years of maintenance, if you're consistently MRD negative, patients are then getting randomized to either continue maintenance, or to stop maintenance.

And hopefully, because the MRD negativity means that you're in a deeper response than just a complete remission, that will mean that there will be a long time before relapse. Possibly some patients may not relapse. And, of course, patients are always happiest and feel the best when they're off of therapy. So the MRD testing may be a way to allow us to do that.

I think the other thing to mention is that MRD testing is predominantly right now being done on the bone marrow, but there are tests in development that are looking at MRD in the peripheral blood. They're not as sensitive yet, but I'm confident that we will improve their sensitivity and that will make it, of course, easier to get and therefore, I think the value of the test will be higher at that point.

Andrew Schorr: Okay. Dr. Fonseca, one of the things I've been reading about is and you used the word earlier, transplant, is whether to do transplant or whether some of these immunotherapy approaches will supersede it. Or whether it matters, whether a patient has it earlier or later. What's the latest thinking at least from your point of view about that, Dr. Fonseca?

Dr. Fonseca: Well, I'm going to try to rope in the transplant question with the MRD question which I was hoping to say, I disagree with that.

Andrew Schorr: Okay.

Dr. Fonseca: I'll tell you why. The reason I disagree with that is we're very fortunate that multiple myeloma have so many biomarkers, hands down as a tumor with the best biomarkers ever. It's not only tumor-specific, is clone specific. And we have been able to historically incorporate these biomarkers into the management of multiple myeloma. One of the most recent examples is the free light chain.

And the question would be, we never requested clinical trials for the free light chain. And I think we have other exciting novel biomarkers, soluble markers. Dr. Berenson has some very exciting data with BCMA. I think this trial should test the worth of an intervention but not the biomarker. Because the reality is, to me, I think the fact that it's prognostic is incontrovertible. The data is out there. We have two men analysis.

I think the question that we're all struggling with is how do you bring that into clinical decision making? And I'll bring this to transplant in a second. And the idea is that most biomarkers are rarely the 100% arbiter of what happen. So we don't have a Supreme Court kind of level biomarker that tells you 100% where you're going, but it just builds on the information that we have on what we do.

And I think that takes me to your question about transplant. I think what we see at this ASH meeting is that no matter how, and that could be with or without transplant that's being tested, just getting to your best response is really the critical aspect. There is some trials that show very interesting data Dr. Gay presented to the FORTE trial with transplant with really great results.

On the other hand, we had the French group that show that appears to be the same whether you do it upfront or delayed. I declare myself still as someone who believes in the incremental value of stem cell transplant for myeloma patients. But as being said, we took 20 years to prove that it was worth it. And then the next 20 years are going to be to prove that we don't need it anymore.

Andrew Schorr: Dr. Orlowski, do you have a comment on transplant?

Dr. Orlowski: I think transplant is still an important part of the standard of care. But I do believe that there are people who achieve, especially if they have good risk molecularly disease at baseline. And if they achieve a very high-quality response, including MRD negativity, the studies that we have available, even if they're not ideal, would nonetheless support the possibility that a harvest and hold approach, followed by maintenance would be very reasonable because the studies that do look at upfront versus delayed transplant, for the most part, show no difference in outcome.

Andrew Schorr: Dr. Berenson, if I recall over the years, I've talked you about transplant, and I said is transplant passe? And I think you were one who thought, "Yes." What's your view with this latest research?

Dr. Berenson: I do not recommend transplant anymore for myeloma. I think the options are multiple. I think that we have to be careful of interpreting progression data with survival data. We certainly know that you can achieve more ability to achieve complete remissions among people who are transplant not. But then you get into the quandary that, yeah, you have a disease, you can't measure a progression in.

So, I think with better sensitivity, with things like mass spec, we may be able to play on the same equal playing field because right now, there are people in complete remission that are progressing. We're not measuring it. And if certainly, patients don't get transplant, they don't

have as many complete remissions. It's easy to measure their progression, I think the soluble BCMA is going to help in that regard as well. But at this point, I'm not recommending transplant. We follow our patients incredibly closely, though, with multiple markers for progression. So I think that does come into play in terms of getting to patients sooner before they're deteriorating. And we do that. I think that helps a lot.

Andrew Schorr: Let's start at the earliest phase, and that is smoldering myeloma. So there's been discussion over the last couple of years about, is all smoldering myeloma alike and who needs treatment when? Dr. Fonseca, so with a patient that comes to you, say well, your myeloma is smoldering, how do you decide whether any of these tests or whatever, how to proceed?

Dr. Fonseca: Well, I rarely favor the side on one visit. I think we're very fortunate that we have the clinical trials, we have models that are looking at risk of progression from smoldering multiple myeloma. But the one factor we all need to keep in mind and we oftentimes have the opportunity to monitor these patients closely. If a person does not have an elevated free light chain, they wouldn't really be at immediate risk for renal damage. And then the remaining significant damage, if you may, is the bone disease. So I tend to observe patients with smoldering quite closely if they're not eligible for a clinical trial.

However, our mentality has changed. In the past, we got a gold medal if you didn't treat too early. But we want to make sure we're not treating too late. So I think there's a boundary there. And that's really part of the finesse in how we approach a patient with smoldering multiple myeloma.

Andrew Schorr: Dr. Orlowski, how do you decide when to pull the trigger on treatment? And for people smoldering or newly diagnosed, how do you decide on what?

Dr. Orlowski: I think Dr. Fonseca made a great point that we have a number of systems that we can use in the smoldering setting to divide people up into high, intermediate, and low risk. One of the challenges is that they don't all agree and you can have one patient be high-risk by one prognostic set, and intermediate, or even low risk by others. And I think that that's a challenge for the field.

If we had one system that we could all agree on, probably the low-risk patients who typically are more like MGUS could be not treated. Whereas, the high-risk patients probably should be just because as Dr. Fonseca mentioned, you can run into problems with things like renal failure and bone disease. It's also important to note that every smoldering patient should get advanced imaging of their bones. A plain bone survey just does not cut it anymore. And you definitely should do either a PET/CT, or a whole-body MRI, or a whole-body low dose CT, to look for bone disease.

In terms of what treatment to select, part of that depends on the molecular characteristics of the patient's disease, and also any comorbid medical factors that they have, VRD or bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone (Decadron) has been the standard of care. And that in part was proven by the SWOG phase III SO777 study. I think the big question is whether adding daratumumab to that will be of benefit. I personally think that it will be and that will be the four-drug standard of care moving forward. But definitely, we need additional data.

Andrew Schorr: Okay. And I should tell people SWOG is Southwestern Oncology Group or it's a research group and you have always been one of the leaders of it, I believe. Dr. Berenson, any comment on when to pull the trigger on treatment and how to start people and this imaging that Dr. Orlowski was saying is so important?

Dr. Berenson: Yeah. Coincidentally, we just pulled our data on our own data set. You guys will find this interesting. BCMA is a really strong predictor of who's at risk to need treatment. Those in the highest quartile, which is the high-risk smolder have an incredibly faster time. And that is independent of the usual other markers. I, for one, tend to probably wait longer than my colleagues. Our median time to progression, even our high-risk group was five or six years, it wasn't two years. I think a lot of us in the field have noted that the number of these high-risk patients that really transfer is probably lower than some of the reports.

So, I tend to watch people pretty long. My indications to treat are obviously, the development of new bone disease, renal dysfunction, cytopenias - but be careful because many cytopenias are not from myeloma anemia, is from iron deficiency, other factors, and we often pull the trigger and I've seen this repeatedly at major institutions or even the bone marrow show absence of iron. And these patients are treated for myeloma and they're iron deficient.

You have to be very careful and be smarter than just assume that every single time there's an anemia, every single time there's a creatine rise, it's not from some nephrotoxic drug or diabetes. There are many causes to these CRAB criteria that are not myeloma related. So you have to be smart, you have to be a good internist.

Dr. Orlowski: I just wanted to echo what Dr. Berenson said. I remember one patient example of a lady that I followed with a community hematology-oncology doctor who had smoldering disease, and then she developed a retroperitoneal bleed and they decided that the anemia was because of myeloma and they started treating her and referred her back to us for a transplant and fortunately, we were able to put the kibosh on that. And she's still smoldering years later. So it's definitely important to look for other causes.

Andrew Schorr: Right. So I want to just underscore for the patients who are watching this. It is so important, I believe, and as we get deeper into this discussion, that complexity of care related to myeloma now in the wisdom you need from a specialist in myeloma, it's really so important to somehow have a consultation, have your case looked at by a myeloma specialist because there are more approved options that we're going to get into now. There are more kinds of testing. And there's a lot in clinical research. And it's easy also to have an inaccurate diagnosis, which is what we were just talking about with Dr. Orlowski.

All right, let's move on. So, Dr. Berenson, we have more approved drugs than ever before, more than happened in the last year since the last ASH meeting. So how do you feel about this? It just seems like you have more options and more potential combinations for people whether they are newly diagnosed, or they need a kicker to their treatment because maybe the initial treatment is no longer effective.

Dr. Berenson: Yeah I think the exciting news here is not only that we have more approved drugs, we have more unapproved drugs that we're using and repurposing and drugs like venetoclax (Venclexta), which we're using, we just are really excited about inpatients not only

t(11;14), which is a translocation that seems to be a [inaudible] response. But when you combine, you can get responses, even among patients who don't have that specific chromosomal abnormality, but also drugs that are being used in other diseases, we are really championing now these JAK inhibitors, which we think are really going to be a home run, and you personally know about those. And we're presenting data at this meeting about single agent, one of them ruxolitinib (Jakafi). And we're now testing a ton in our lab. And I think these drugs, as you probably know, personally are so well tolerated. And we really have to think about that as we're administering drugs.

You're talking about people that are no longer hanging on the cliff to survive. These people are living, not only for years, but now hopefully, decades. They want to have quality of life. They don't want to just stay alive. And I see that every day in clinic.

Andrew Schorr: So Dr. Orlowski, let's talk about that. So there are two, three, four drug combinations now in myeloma. So again, how do you sort this out, and then that may include drugs that were approved for other cancers as Dr. Berenson was just talking about.

Dr. Orlowski: You have to take a look at a number of factors in deciding on therapy that includes the molecular features of the disease, how aggressive it is, what comorbid medical problems the patient may have, and also, what the patient's preferences are in terms of therapy, whether it be oral, or intravenous, or subcutaneous. I think the good news, as you're mentioning is that we have a number of doublets, triplets, and quadruplets.

In general, I think most of us in the field prefer especially in newly diagnosed patients to go with either a triplet or a quadruplet because that's the time when the disease is most sensitive. And if you give a drug second or third line, it's probably not going to work as well as it does in first or second line. The problem is that, of course, the more drugs you use, the greater the risk of toxicity.

I certainly agree with Dr. Berenson about venetoclax being a great drug in the t(11;14) translocated patients. And there are some folks without t(11;14) that have high BCL-2 expression, but the one studied the BELLINI trial that was done did also show that for the people that didn't meet those criteria, there was a higher death rate.

So, I think we do need to be careful in repurposing drugs. I do agree that JAK-STAT inhibitors are really a clear, good area to look at because of the importance of IL-6 signaling in myeloma which goes through that pathway. But not every drug from other diseases can be repurposed. And the other example that we could probably pull out is the pembrolizumab (Keytruda) data, the PD-1 inhibitor, which unfortunately with both lenalidomide and pomalidomide (Pomalyst) showed an increased mortality. So we do have to be careful.

Andrew Schorr: And what you're talking about is one of these checkpoint inhibitors that's had great utility in lung cancer and melanoma, would it apply to this blood cancer and it seems the answer is no.

Dr. Orlowski: At least in combination with immunomodulatory drugs. Now, other checkpoint inhibitors and other combinations are probably still worth looking at.

Andrew Schorr: Okay, Dr. Fonseca, so, when we talk about hitting myeloma hard, maybe with four drugs upfront, that's a lot of treatment for people. And sometimes, people get to a point where they've been heavily pretreated. And then you say, well, gee, are there options for them when things start to fail? So let's talk about that into the continuum too. You have a lot to help people with, maybe for decades, as Dr. Berenson said, but sometimes then the myeloma is getting the better of it. It used to be that there wasn't a lot to do. But it sounds like there is more to do now.

Dr. Fonseca: There's a lot more to do. And let me just say a couple of points there. One is that one of the biggest burdens of myeloma for patients is, of course, the very long duration of treatment, for instance, like we do with maintenance. And we have to think or I think that we're close to an era where we might be able to implement upfront, highly effective therapy. And then, if we could do that, with induction with or without transplant, maybe with immunotherapy consolidation, you can get rid of all cells. I don't think it's going to be unreasonable to test strategies that don't require that long term treatment.

So, I know we're going through a lot of studies and combinations. But it is not impossible to think that we might have in the near future, something like the equivalent of an RCHOP for lymphoma, where you just do one treatment, and you're done. That's not the case right now, should be very clear.

But number two is when you look at your drugs, you have to think like the coach of a football team. You have to put your best players always and pick your best players, and they display the players that are not as good because we've published a paper just in the last year where we show that with every subsequent line of therapy, not everyone gets the opportunity to try the next line of therapy. There's a lot of attrition.

For patients who are not transplant candidates, that attrition is 50% per line of therapy, and for multiple reasons. But as they go into the second and third, disease progression or fortunately, passing because of the disease becomes more and more common. So, you need to put your best team right from the get-go.

Andrew Schorr: And that's what Dr. Orlowski was talking about is these combinations. But then, so you have people who may be older, Dr. Fonseca, frail, they've had a lot of these treatments, the treatments either weren't as effective as you hoped, or are no longer working. And then you hear about things that are still experimental, CAR T or other kinds of immune approaches. Is this a promising option for them?

Dr. Fonseca: Well, I think and we learn a lot in myeloma as we go forward, how to adapt those, adjust, and then select the treatments that will be able to be used and those that don't necessarily have the health or the stamina, patients that are frail. And we're seeing that with all these drugs. I don't think there is a consensus that someone who is not eligible to stem cell transplant won't be able to derive benefit from some of these other T-cell engagers. So in fact, they're being tested.

And even some of the drugs that are novel, a great example, a drug that went off through a choppy start selinexor (Xpovio), with a proper dosing and the proper, I'd say, medics, I've used it now in the elderly as well too with good results and in combination. So, there's a lot of learning

that happens after the fact that allows us to use some of these treatments in the more advanced population.

Andrew Schorr: Right. And CAR T, chimeric antigen receptor T-cell therapy. There are so many uses of that. And then there are other improvements being made to that as well. Do you want to comment on that?

Dr. Fonseca: Sure. I think we're learning that there's different rates of CRS, the [inaudible], the neurotoxicity as well too, and our approaches to try to ramp up. We saw beautiful presentation by Dr. Costello from UCSD on a novel approach using transposons and doing one of their CAR T-cell models. So I always tell my patients, as we wait for this, people are ironing out the wrinkles of the CAR T-cells and that's been really the case with every single myeloma drug as we learn more, we know how to use it in a safer and more effective way.

Andrew Schorr: Okay. And CRS by the way, folks, cytokine release syndrome, an effect of CAR T. What about you, Dr. Berenson? So, we talked about transplant, you're not a fan of it. But now we have this other approach on the horizon and maybe improvements to it, CAR T, what's your take on that?

Dr. Berenson: Well, that was my first work with Dr. Pfeffer Thomas in Seattle 46 years ago as a med student to show that T-cells kill tumors in mice. I certainly think that that's an option I think, we have to be careful about when to use it, how to use it, and the cost of it and the durability of the responses. I think it's a work in progress. But I don't know how generally applicable that's going to be in the community until it's made simpler.

So, I think we'll see what the future holds. Certainly, we're seeing responses. They're certainly not as durable as we would have hoped. I think some of that is secondary to the myeloma ability to actually induce immune suppression. This is a major problem in myeloma, and certainly, will be a problem as we get these patients in the vaccination mode. I think many of them under the false assumption that they will be immunized just like us, and I don't think that's necessarily going to be the case. And I think they really need treatment. And I certainly, am a strong advocate that we don't give up on treatments for this ugly virus that we just assume all will be merry with vaccinations because I don't think that's going to be true in our patients, unfortunately, at least most of them.

Andrew Schorr: We're going to talk about COVID specifically in immunocompromised patients in just a second. Dr. Orlowski, a comment from you for sicker patients, if you will, CAR T-cell therapy or other immune approaches. What's your view of that?

Dr. Orlowski: I just like to give a slightly different opinion from Dr. Berenson. It sounds that he's not very enthusiastic about the CAR T-cells. And it's true that we're not seeing a plateau, meaning people don't seem to be cured as they were for the CD19 CAR-Ts for lymphoma. But the flip side is that we're getting higher, complete, and overall response rates and longer durabilities than we've ever seen in relapsed refractory disease.

And this is in patients who have had more therapy than we've ever given before. And there really is no other approach that we have available to us that would do as well. So my level of enthusiasm is much higher, I think as we move it earlier, where hopefully, patient's T-cells will be more robust, and the disease resistance will be lower, it will work even better. There are

some patients who will not be transplant eligible, and yet may still be eligible for CAR-Ts although there also will be people who will not be eligible for either.

And for those who are not maybe something like an antibody-drug conjugate going after BCMA, which has a relatively easier toxicity profile than a CAR T would be one way to go. And the bispecifics also look, I think, quite attractive. So I think there's a lot of reason for excitement and optimism.

Andrew Schorr: Before we go on, I just want to see if I am explaining CAR-Ts well. And that is chimeric antigen receptor T-cell therapy, but basically, where you're making a drug out of someone's T-cells, and I guess, is it combining it with a virus that targets and goes back and attacks the myeloma? Did I get that right, Dr. Orlowski?

Dr. Orlowski: Well, the virus essentially is a way to get a new gene into the T-cells. That gene is what results in the receptor being expressed. And the receptor then recognizes a protein on the myeloma cells that allows the T-cell to hone in on the best target. So, it's really a way to, if you will, train the T-cell to go after myeloma, and hopefully, only the myeloma cell and no other cell.

Andrew Schorr: Okay, right. I always think of it as training a bloodhound, giving it a scent, and then saying, "Go get it." And the bloodhound does.

Dr. Berenson: Very good analogy.

Andrew Schorr: Thank you. So let's talk about BCMA for a second. And Dr. Berenson, we've talked about that before. So Dr. Orlowski has mentioned BCMA. And now they're these anti-body drug conjugates that use BCMA. So this is trying to have a more powerful approach to go after the BCMA as a target on the myeloma cell and have a bigger bang. There's a new drug, for instance, approved for that. Is that an important development?

Dr. Berenson: Yeah. Well, I think certainly, anytime you can target the cell, a la rituximab (Rituxan), is a good thing to do. I don't think that's going to be the final answer because we know that cells outsmart these antigens over time, don't express them or figure out a way around them, but it's certainly another option. And I think the ability to piggyback drugs on top of it, I don't necessarily think that what you're talking about is the right one. But, being able to target drugs that will be concentrated on tumor cell is a great thing.

So, you get two bangs for your back about targeting the cell and helping the immune system but also piggyback on top a, if you will, a cyanide, that's going to poison only the myeloma cell and be concentrated there.

And I think that's really the future is my good friend, my wife, the actress, taught her on stage. It's not about more, it's about the more specific, and I think this is the beginning of that road. And that journey is going to be a long one. But ultimately, I think our goal is to kill the myeloma and only the myeloma.

Dr. Orlowski: And Andrew, along the lines of your analogy, in terms of the bloodhound, the way I described the antibody-drug conjugate is that it's like the Trojan horse. You have this antibody

that binds to the myeloma cell. The myeloma cell says, "oh, gee, this is interesting," and takes it up inside. And then once it's inside, the drug that is linked to the antibody can then kill the myeloma cell.

Andrew Schorr: All right, How do you feel about the monoclonal antibodies? We have, I think, at least two or three that had been approved in the last year, you have more antibodies now than ever before, Dr. Orlowski?

Dr. Orlowski: Well, I think the great thing about antibodies is that they're very specific. And unlike small molecules, which can get into any cell in the body, the antibodies are very selective, so they tend to have a much more favorable side effect profile. And, of course, we now have two anti-CD38 antibodies. We have one SLAMF7 antibody, and we have the BCMA antibody that we've talked about called belantamab mafodotin-blmf (Blenrep).

And I think we're only just beginning to have the capacity to use antibodies. I also think it's great that we're using the myeloma cells against themselves because actually, myeloma cells are the ones that make antibodies. And now we're using the same antibodies to go after the myeloma cell. So it's a little bit of a turnabout is fair play situation.

Andrew Schorr: Dr. Fonseca, we have this class of medicines, the monoclonal antibodies, Dr. Orlowski has discussed it. So if we have several now, how do you decide which antibody should be in combination for which patient?

Dr. Fonseca: So I think it's worth taking a pause because we have different types of antibodies. We have those that are considered naked antibodies like isatuximab (Sarclisa) and daratumumab in their various formulations. Then we have belantamab, which is a conjugated antibody that, as we've heard it considered like a Trojan horse, it brings the toxin inside the cell. And now we have a set of antibodies that elicit that T-cell response, the so-called bispecific antibodies. And that was really one of the highlights of this meeting, seeing all those bispecific antibodies coming forward.

So, I think just to say how we position them is going to be hard. And also, I allude to the fact that I think it's hard to talk about BCMA therapies. BCMA is just a target. And we've heard about other targets like FcRH5, and it's more important to think about the mechanism of action. And I think that's really what's going to drive how we select those antibodies. We're very fortunate that we've been using now for quite some time daratumumab. And it has really been transformational in our ability to provide deeper level of responses for our patients. So I just can't wait to see how we're going to start sequencing all these antibodies.

Andrew Schorr: So Dr. Berenson, I've been through leukemia therapy, a combination therapy, and my doctor explained that the different types of drugs would hit the cancer cell from different directions to try to knock it out. So is that where we are with myeloma that once you begin therapy, the argument for these three and four drug combinations or different new kinds of monoclonal antibodies is to try to hit the cancer cell from different directions?

Dr. Berenson: Well, it's even more exciting, Andrew, because now we're learning the mechanisms that these drugs elicit can boost the activity of other drugs, we just saw a paper come out in *Blood* in the last few weeks, for example, with my favorite drug right now ruxolitinib upregulate CD38, voila, that's the target for isatuximab, for daratumumab. So we're actually

seen a drug that's active in myeloma, at the same time makes the target CD38 more easily accessible from antibody.

Also, I would really advocate that as we combine drugs, we begin to see that we can use them at lower doses. For example, the BELLINI trial using venetoclax, at 800, 1200 milligrams, oh my god, we're using 100, 200-milligram doses of this drug, and seeing complete responses in many patients in combination. So you don't necessarily have to use these drugs at toxic doses as you combine them together. You can tamp them down and they can be highly affected.

Andrew Schorr: So Dr. Orlowski, so it sounds like you have more notes on the piano you can play, as you do more sophisticated testing. And then, Dr. Berenson was just saying, as you learn that it's like how hard do you press the notes? In other words, what's the smallest dose that's still effective to reduce side effects, higher quality of life, etc? Is that where we are?

Dr. Orlowski: Well, I think it's definitely important to try to minimize dosing as much as possible to avoid toxicities. At the same time, we want to make sure that we're hitting the target appropriately. I think one of the concerns right now is that we don't really have good assays that we can use in patients to know how well we're hitting the target.

And antibodies, for example, I think we would probably all advocate given that they have a relatively good side effect profile, that we not reduce the dosing of those drugs. Because, for example, with CD38, which we've talked about with both daratumumab and isatuximab, there is CD8 on not just myeloma cells, but also on some other cells. And you want to make sure that you've essentially covered all the CD38 on the myeloma for maximal efficacy.

Andrew Schorr: Dr. Fonseca, any other comment you'd want to make about dosing and basically quality of life as well?

Dr. Fonseca: I agree with everything that has been said, and one of the challenges is that all of this has to be tested empirically. Traditionally, as your audience knows, we do this phase I studies to determine the right dose, but you cannot do every single combination in a phase I study, it's just literally impossible. So a lot of us want to find that right does that preserves quality of life and still is efficacious. And I think it's just fair to say it's an imperfect process. And we recognize that there's a significant burden in the quality of life for patients with some of the toxicities.

For instance, right now, I have [inaudible] bonnet with a peripheral neuropathy that we see with a Velcade and it's a significant problem. We need to continue to work to find better ways to use all of our medications. So I've mentioned before, we almost find ways to make it better. And we can say we're doing it better than we did it in the past. But that's not to say that these drugs don't continue to have some significant toxicity.

Dr. Berenson: But one of the best examples is probably dexamethasone. Back in the old days, we used to do 40 milligrams for days, one through four, nine through 12, and 17 through 20. We did it because it was one of the few drugs that we had. And people took it because that was the only option. But now we give it once per week, and people do much better. So I do think that the effort to learn how to optimally dose these drugs is important as long as we're not also compromising their efficacy.

Andrew Schorr: And Jim Berenson, you've talked about dexamethasone for years on reducing it or not going in that direction.

Dr. Berenson: I would chime in here that it's not only the dose, it's the schedule, it's the drug. Steroids are so different. For example, methylprednisolone, we use instead of dexamethasone in our clinic, because we find it such a much better-tolerated steroid for patients in terms of mental function, in terms of insomnia issues. And we give every other day dosing, we don't give once a week dosing. So, I think it's not only the drug and the amount, the schedules need to be played with.

We're seeing this now with Xpovio, selinexor, the new drug. It's a very different drug at lower doses. And I think that we're just playing with schedules now in our preclinical modeling. So I think all these things matter. It's not just the amount. It's the specific drug, the schedules, how long you give them. These things as said by Rafael become almost empiric in individual patients. I have such varying dosing and schedules of steroids among so many different patients, their tolerability varies incredibly, with this class of drugs.

Andrew Schorr: I want to talk about just a couple more things before we go. One is about disparities among racial groups or economic groups, etc. And I think, Dr. Orlowski, you've presented about this as well. So first of all, we have a higher incidence of myeloma is my understanding among the African American community. But often, people don't get some of these treatments we're talking about that have been great improvements. So how do we attack that? How do we make a difference so that all patients get the myeloma treatment they need and deserve, Dr. Orlowski?

Dr. Orlowski: Yeah, that's a great question. And you made the point that African Americans have twice the rate of not just myeloma but also precursor diseases. The good news is that if they get novel agent-based therapy, and also stem cell transplant, many studies show that their outcomes are the same as if Caucasians have the same therapy. And actually, one or two suggests that their outcomes may be actually even better.

So, I do think that trying to make sure that everybody gets access to novel drugs is really the key here. And that would be something to look at, at a national level. I also think that among the African American community because of the history of research and medical research, in particular, are not always being very positive in this country, that they are a little bit more hesitant to go on to clinical trials. And I think an effort needs to be made there because we, fortunately, weeded out all of the ethical problems that there were in the past, with informed consent that's now available. And trials often give you access to some of the best and newest therapies before they're FDA approved.

In general, often we find that people on trials do better than people who get just standard of care therapies. So I think that's another aspect to keep in mind.

Dr. Berenson: Yeah. There was just the discussion this morning, actually on CNN, from the head of the NAACP about the participation of African Americans in the vaccination trials and their fear, because of the Tuskegee experience, they are very scared. And we see that, I'm sure you guys see that, I see that, that African Americans are, "Wait a minute, I'm not going on trial.

You're using me as a guinea pig." And I think we've got to try to deal with that on a national level.

Andrew Schorr: Right. Dr. Fonseca, any other comment from you about trials both for African Americans, Caucasians, Asian, Latinos, etc., about with all this stuff happening in myeloma, the importance of doctors and patients discussing trials and patients considering it.

Dr. Fonseca: Yeah, I think the work your team does and others in raising awareness and how clinical trials have moved the needle and help advance our ability to treat myeloma further is just, without a question, a great story of success. I'm pathologically optimist. So I'm going to say that with what we have seen with a transformation of medicine to partly a virtual and endeavor where we can reach patients remotely, I think this is actually something that democratizes in some way medicine, because I think you've said it before, people should try to seek a myeloma expert, but sometimes traveling 500 miles and the gas and a day at a hotel and meals can be a substantial expense for a family or if a caregiver has to take days off of work. So they're going to think about that.

And if we can really maximize their ability to now go out and reach out all communities that could benefit from myeloma expertise, be that in some of the underserved populations, be that in rural areas as well too. I hold, as I mentioned, the cancer center directorship at Mayo Clinic. And this is really one of our commitments, we want to make sure we have impact and relevance to the communities we serve. And I think things like this, like this video conference, hold a potential to expand that reach.

Andrew Schorr: Right. And one point I'll make just about expense for people. If you're in a trial, the trial drugs are not a cost to you. And they're often other things that go along with the trial that are not a cost. And there is assistance often. And more and more, these leaders in the field are trying to consult with community oncology doctors, so that their trials that are being done closer to home, as well. So all things to consider.

The last thing I just wanted to talk about with you is what Jim Berenson alluded to, and that is as we're doing this program, we're in the midst of the COVID-19 pandemic. We're now at the point where please God there will be vaccines for people, but we know that myeloma patients are immunocompromised. So the question is, do I go forward with myeloma treatment? And I think Jim Berenson, you were saying, "Yes, for sure." And do I also get vaccinated and can I hope for an immune response, even though I'm immuno-compromised? So, I want to ask each of you about that. So, Jim Berenson, you want to tackle that first?

Dr. Berenson: Yeah. So I certainly am a firm believer that these patients must continue therapy, and I certainly haven't backed off at all. We've had several patients contracted, we've had several staff members get it. Unfortunately, one patient did succumb of it in Las Vegas. And interestingly, he was actually getting treated on a ruxolitinib trial, which some of you know is now being used to counter the overzealous inflammatory response. And unfortunately, the doctors in the hospital wouldn't continue it. So that was really an unfortunate irony with that particular patient.

Other than that, the other patients have gotten through it. There's some belief that perhaps the lack of immune system may be an advantage because they don't have this hyperimmune

response. I don't know if that's true or not. I am concerned though, that again, as we move into this vaccination phase, my patients lacking normal antibodies that is not the myeloma antibody, will be indicative of their inability to respond to a vaccination. We've certainly seen that as all of us know in the myeloma field with the shingles vaccines, with the flu vaccine, it's only a minority that really matter a response, and that will probably be true here.

So, I don't want people to get the false impression that as soon as they get vaccinated, they're going to be able to go about their normal activities until we tamp down this virus nationally. That's my feeling.

Andrew Schorr: Dr. Orlowski, how about you?

Dr. Orlowski: Well, I do think that there are some patients who, for example, if they're in complete remission and MRD negative and getting some kind of parenteral therapy could probably switch to an oral regimen. But if you have active disease, then definitely, the myeloma is the greater risk to your health. And we should do everything that we can for patients like that. I share Dr. Berenson's concerns in terms of whether patients will have the good robust immune responses to the vaccines. We've seen that with influenza vaccines and with pneumonia vaccines, but it's definitely still important that when the COVID vaccine is available, every patient with myeloma get it.

There is a theoretical possibility that those folks that are on immunomodulatory drugs may actually have a slightly better response. And that therefore, there may be enhancement. But even if you only get a 50% of normal response to the vaccine, first of all, that may be enough to prevent you getting the disease, or at a minimum, it may be enough to make the COVID course more benign than it otherwise would be.

But I would recommend anybody that gets the vaccine still continue with the same measures; the hand washing, the mask-wearing, and the social distancing because we do need to make sure that there are enough people vaccinated, and that the caseload goes down to such a level, where hopefully, everybody's risk of exposure will be very low. So even with the vaccine, you should still continue with the same precautions, at least for a while.

Andrew Schorr: Well said. Dr. Fonseca, I want to give you a shot at this as well.

Dr. Fonseca: Thank you. I'm not going to say anything more about therapy. I agree with my colleagues, and I was going to say the same thing about the potential with IMiDs. There's at least two published papers in that regard. But I'd like to add something. If you're wondering, can I get the vaccine? The answer from my perspective is a resounding yes. The vaccines, at least, from what we're seeing are RNA vaccines. So the risk to you is essentially nonexistent. It's not like the vaccines where you have an attenuated virus that we're concerned about people that have low immunity that are immunosuppressed.

And given that... Yes, there are considerations that they may not mount the same response, and our patients, in particular, will need to be careful, I think the upside is much greater. So, go ahead and get your vaccine. Now, I'll put a shameless plugin, at this meeting, we're presenting an abstract on titers, so again, childhood infections that we did on patients with transplant, the novel therapies. Unfortunately, a lot of patients still keep those titers even before immunization.

So I'm hoping that our immune system ultimately will prevail through all of this, but until we bring the numbers down at the national level, one has to continue to be careful.

Andrew Schorr: Okay. I want to just end by a closing comment from each of you. So we have viewers, families who are affected by myeloma, the patient themselves, or a loved one, different stages of the disease. As we look back on ASH 2020, where are we now, and what is your message for these families? Dr. Berenson, let's start with you.

Dr. Berenson: I think it's a time of great hope, and great advancement, better quality of life, better supportive care, we know a lot more how to use these drugs and make these people's lives ones as we like to say live their best life possible. I think we're seeing that today much different than we used to. Supportive care is really important. We know how to use these drugs much more effectively. So I think it's a message of hope. It's a very positive time, survival is improving, quality of life, people can get their lives back together, and their families and friends as well can enjoy them in a better way.

Andrew Schorr: Dr. Orlowski.

Dr. Orlowski: I'll be even more optimistic and say that with some of the immune therapies that are first being reported at this ASH meeting, and as we move them earlier in the disease process, I think that these will contribute to our ability to actually cure at least those with standard-risk myeloma within the next 5 to 10 years. And I'm hopeful also that the high-risk patients will do substantially better. And I'm looking forward to see how Dr. Fonseca will be even more positive than that.

Dr. Fonseca: It's hard to top that but I agree, I share the word cure with my patients is a small fraction still. But we don't know, as we evolve, and more and more patients are getting into deep responses, MRD negative, and those seem to be sustained. I think we're going to see great progress. And my hope is that our progress has been going from here to here with level of responses. Now we have to go from therapy from here to here because we have the right therapy. So I think those two boundaries will be determined by MRD. And I really hope for a future where we can do that with not very prolonged therapy.

Andrew Schorr: Wow. That's a wonderful message of hope. And I've been interviewing you, gentlemen, over the years. And I definitely see progress. There's more to talk about. And I think you have patients who are living longer and living better, even people with the most serious versions of myeloma, there are options for them too. So it's a great message. I want to just remind our audience that we continue interview these experts and others throughout the year, and so it's not just the ASH story, but it's the incremental story during the year, which continues to change. So please look at www.patientpower.info for all of that, and those updates.

I want to thank each of you Dr. James Berenson from Los Angeles and your institute there. Thank you for your more than 40 years of work in myeloma. Dr. Robert Orlowski from MD Anderson, thank you for all you do there at MD Anderson and helping lead research around the world. And also Dr. Rafael Fonseca from Mayo Clinic. Thank you for being with us as well. I'm Andrew Schorr. Remember, knowledge can be the best medicine of all.