ASCO 2019 Highlights: Advances in Multiple Myeloma

ASCO 2019 conluded on 4th June 2019 and we are excited about Multiple Myeloma updates from the largest gathering of oncologists, researchers and health professionals. The myeloma panel is talking to Dr. Joseph Mikhael, Professor, Applied Cancer Research and Drug Discovery, Translational Genomics Research Institute (TGen), City of Hope Cancer Center and Chief Medical Officer, International Myeloma Foundation on advances in research, treatments and new myeloma programs that are on the anvil.

Full Transcript:

Priya Menon: Good evening everyone and welcome to Cure Talks. This is Priya Menon, your host and today we are discussing multiple Myeloma and we are so excited, the largest gathering of oncologists, researchers and health professionals, the annual meeting of the American Society of Clinical Oncology 2019, just concluded yesterday and we are looking forward to hear the research updates from the meeting. And giving us a view and providing us with information is none other than Chief Medical Officer of the International Myeloma Foundation, Dr. Joseph Mikhael. Dr Mikhael welcome to Cure Talks. It's a pleasure to have you here with us.

Dr Joseph Mikhael: Oh, it's absolutely my pleasure to join you today.

Priya: The Myeloma panel talking to Dr Mikhael today include advocates and survivors, Gary Peterson, Cynthia Chmielewski, Matt Goldman and Dana Holmes. Gary will be co-hosting and leading the discussion. We will also be addressing questions from the audience towards the end of the discussion. You can post your question on curetalks.com or email it to priya@trialx.com. For asking your questions live, please dial in using (718) 664-6574. We have quite a bit to cover today and we are getting right into it. I will now handle it to Gary to introduce our expert and begin with the discussion. Gary you are on.

Gary Petersen: Thank you, Priya and thank you so much for providing this venue for the Myeloma patient community. I am just honored to have the Chief Medical Officer for the International Myeloma Foundation, Dr. Joseph Mikhael. He works closely with the IMF – International Myeloma Foundation's Chairman and to advance the mission of the organization and research education, advocacy and patient care to improve the lives of patients with multiple Myeloma. He was selected for this position from a world of Myeloma specialist because Dr. Mikhael has a tremendous passion for education, travels the world lecturing and develops collaborations in the Myeloma community. Previously Dr. Mikhael was hematology oncologist at the Mayo Clinic in Arizona where he researched, taught, treated multiple Myeloma and related conditions. He also served as the associate dean of Graduate Medical Education and the deputy director of Mayo Clinic, Comprehensive Cancer Center. After completing medical school and residency at the University of Ottawa, Canada.

Gary: He completed a residency and fellowship at the University of Toronto and the Princess Margaret Hospital in Toronto, Ontario. Dr Mikhael also served as a counselor on the American Society of Hematology Executive and is involved in monitoring the next generation of hematologists. In addition, Dr Mikhael is also putting on his plate, continuing his work in clinical and academic medicine with the City of Hope Cancer Center. So a lot going on with Dr Mikhael. And so happy to have you with us.

Gary: I grew up in Wisconsin. I'm in Wisconsin right now. So, so obviously I was a close neighbor, originally. What I like to do now is to get into the questions and the first of which is, there are a bunch, it seems like there's one every week, but I don't know, cancer meetings in the world each year and some of them have a focus on Myeloma and some do not. And so, which, which are the most important for Myeloma patients to observe, to follow, to watch?

Dr Joseph Mikhael: Thanks Gary. What a kind introduction as I usually say, people just need to know, my name is Joe and I'm here to give the talk type background, but that was very kind of you. I think it's actually a great question because it speaks to what's happening in Myeloma that Myeloma has really been revolutionized over the last decade. I mean, had we had this conversation a year ago, I basically would have told you that we have one most important meeting a year of the American Society of Hematology annual meeting, which always takes place in December. As you mentioned, I have the privilege of being on the executive of that organization and that was really the overwhelming majority of where myeloma would be presented. But we have really seen a growth of that over the last several years such that this meeting we just had, which is of course the largest cancer meeting in the world of 50,000 people at ASCO or the American Society of Clinical Oncology also has a lot of Myeloma and presented at it.

Dr Joseph Mikhael: And then to add to the trio, we also have a meeting next week in Europe, the European Hematology Association meeting in Amsterdam, and we're also anticipating some very good discussion there, although there is, tends to be a fair amount of overlap between what happened last weekend, this past weekend at ASCO and it will happen next week at EHA. So for the Myeloma patient community and just for the Myeloma community in general, you really need to have ears to the ground for these three major meetings. But frankly there are others that come along as well. We have the International Myeloma workshop that happened once every two years that will be taking place this year in September from September 11th to 15th in Boston. And often a new research and deeper discussions around features of myeloma are discussed. And then lastly, of course, you mentioned in my role as the Chief Medical Officer of the International Myeloma Foundation, at the meeting next week in Europe and also at the American Society of Hematology meeting, we have to live broadcasts with myself, Dr Dury and one or two other guests where we discuss the latest research as well. So I think if a myeloma patient can tap into those, not to mention the 24/7 Twitter feed of myeloma, then hopefully they can keep up with so many of the great things that are changing in this disease.

Gary: Okay. Well, we have a couple of heavy hitters with the Internet. That would be myeloma teacher Cynthia Chmielewski and Dana. Dana Holmes is brand new, so not to the Myeloma patient community, we would love to welcome you certainly to this program and we're just so happy to have her here and representing the smoldering group of Multiple Myeloma patients. The thing is we just had ASH not too long ago and now we have the new one, ASCO, did you see a general change in the direction or a shape in the direction for the treatment of Multiple Myeloma?

Dr Joseph Mikhael: That's an excellent question, Gary. Thank you. I would say that there's a constant shakeup. I mean, we are, and as evidenced by the abstracts that were just presented at ASCO, and I know we're going to dive in a little bit deeper to them, but to try and give people the balcony view, the shakeup is at all aspects of Myeloma, which is to say this, the very heart of its diagnosis, distinguishing smoldering from active Myeloma. So there's the diagnostic side, if you will. Then there's the early intervention. We had some great shakeup as in your words over this last year about whether or not should we be jumping in earlier or not. And, and we can discuss that a little bit more. We get to the abstract and then we've seen significant change. This has probably been one of the greatest changes in this last, this revolution of Myeloma in the last year to see a lot of things changing in frontline myeloma where now we're seeing the greater incorporation of monoclonal antibody drugs like Daratumumab.

Dr Joseph Mikhael: And then lastly, we're absolutely a lot of very interesting findings in very relapsed multiple Myeloma. So with the CAR-T cell therapies with these new, what are called bispecific antibodies. So, it's hard for me to think of an area of Myeloma that isn't currently being improved and worked on to benefit our patients. And so we, we literally do need these three or four meetings a year because a lot happens in between. If you have a new cycle where you're only ever listening to morning news, you're gonna miss a lot during the day. A lot of things happen during the day. And so in the Myeloma world, we have this constant turnover and this last meeting was clear evidence of that.

Gary: That's quite a change unto itself because it seems like there for many, many, many years. We just had like three or four different classes of drugs and nothing else was happening. And now all of a sudden

there's something of an explosion. But we're going to talk a little bit about that. The next part, which is of the abstracts presented at ASCO, which do you find to be some of the most interesting and why? And it's important, we know and we understand that the IMF has got their fingers in a lot of stuff and that this is probably one of your major focuses. And as a result, you know, we certainly now that you're, the meeting is over and everybody has had a chance to try to digest what has come before that you have an opportunity to provide us with a tremendous opportunity for understanding from a patient's perspective. What kinds of things are happening for the future?

Dr Joseph Mikhael: Yeah, absolutely. And I think the way I would structure my answer for this, Gary, is to think about what is most likely to immediately or in the very near future affect patients and then what is going to affect patients a little bit further down the line. Because sometimes when a patient is being exposed to all of these different research articles and things being discussed, it's hard to filter them. You might think, oh my goodness, this sounds so great. Is this coming to the clinic next week? And so I think the way I would put it is this, I fancy that we could just look at at five things really quickly. So, number one is we saw a lot of evidence and discussion of using Daratumumab more fully in the earlier settings. Now we did have Daratumumab approved technically with a combination that we don't normally use bortezomib and Melphalan last year, but now we saw a New England Journal paper publication just last week and another presentation at this meeting where we're starting to see Daratumumab come up front.

Dr Joseph Mikhael: And probably the immediate way to think about it Gary, is that as you mentioned for so long we had the old school chemo, proteasome inhibitors like Bortezomib and Carfilzomib. And then we had immunomodulatory drugs like Thalidomide and Lenalidomide, Apolidomide, and historically for frontline therapy we took initially one and now two of those newer drugs, one proteasome inhibitor and one immunomodulatory drug and combine them somehow. And that's how we treated people front line. Well now we have a whole new class to add. So now we've got sort of, if you will, three big choices, the proteasome inhibitors, the immunomodulatory drugs, and now monoclonal antibodies like Daratumumab. And now we're seeing that in the very, very near future, like in the next couple of months we're really going to be end up saying to most patients, all right, which two out of the three is best for you?

Dr Joseph Mikhael: Should we still go with the Bortezomib, lenalidomide combination upfront or should we use a monoclonal antibody and lenalidomide up front? So I think that's going to be the most immediate change that we're going to see now you've got out of these three drugs, we'll take two. If I can move thinking further ahead in that same vein, probably within a year from now we may likely be actually using quadruplets in frontline therapy. We're actually just going to use those three drugs together plus steroids, what we call a clod and use them all together. So someone will get something like Daratumumab, Bortezomib, lenalidomide and Dexamethasone, and that might sound like a big hammer, but we're starting to appreciate that if we treat myeloma very effectively upfront, people can have a much longer remission and do better in the long term. And so we're still waiting on them on the data to mature.

Dr Joseph Mikhael: So that's not the instant thing for using those quadruplets or those quads. But I see that in the not so distant future. The second abstracts that I found particularly important that we know it's coming. We've been talking about it. This may be the most patient centric study of all of ASCO. If I was about to address a group of patients and someone said you could only talk about one abstract Joe, which one would it be? It would be the phase three trials, a very big study comparing, giving Daratumumab intravenously versus Daratumumab subcutaneously. Many of the patients even listening in I'm sure have been on Daratumumab and the first eight, nine or 10 hour infusion are now getting Daratumumab either weekly or every other week or once monthly for four or five hours.

Dr Joseph Mikhael: They've now created a formulation of Daratumumab where it's given for five minutes subcutaneously and it's amazing and it was just as effective as regular Daratumumab and dramatically less of what we call those infusion reactions that people can get when they get Dara. So to me that's number two in our five steps here where I really think this is going to affect patients. The third interesting abstract was presented and I had the privilege of doing the very first in-human study for this drug was a drug called Isatuximab. I know it's hard to get used to all these new names, but Isatuximab is basically another version

of Daratumumab in that it has a similar mechanism of action as a monoclonal antibody and it is quite likely going to be one of the, if not the next one or the next two drugs approved, new approved in Myeloma.

Dr Joseph Mikhael: It's not a new class as a whole, but we've also learned it's not just about getting a new classes of drugs that's about getting new drugs within each class. And so although …

Gary: What was it was originally called, for those who might not know..?

Dr Joseph Mikhael: It might have a lot of different names, it was called SAR with numbers after it. And there was a few iterations of that. So people often call it SAR, over the last four years now it's been known as Isatuximab. Now they all end in Mab, meaning monoclonal antibody. And so this drug was presented as being combined with pomalidomide and it'll likely be approved within a year to be used in combination with pomalidomide in patients with relapsed Myeloma. I'd say the fourth set of discussion points that are interesting was the area of smoldering Myeloma. We're redefining the disease.

Dr Joseph Mikhael: I tell patients, we used to define this disease as someone already had to have damage to their body or to their bones or their kidneys. It's like saying, if I'm going for a run today, I'm only going to stop my friend from falling off the cliff once they're falling off the cliff because only then do I know they're in trouble. Well, no, no, no. I don't want to do that. I want to pull them away before they get to the cliff, and so a few years ago we redefined myeloma to say, wait a minute. You don't just need the so called crab criteria or a calcium elevation, renal or kidney damage anemia or low hemoglobin or bone disease. If you have a few other potential events, it tells us that maybe your kidneys aren't damaged yet, or maybe your bones aren't damaged yet, but it's on the way, so you're getting close to that cliff, let's pull you back.

Dr Joseph Mikhael: And so we have some interesting work redefining how we think of smoldering and even a study examining maybe those people that are highest risks, those are the ones that are running fastest to the cliff. Maybe we can treat them early on and prevent the disease or at least delay the disease. I don't think there's consensus yet that that's what we're doing, but we are trying to better define the line of when people should treat and not treat. And then lastly, I'll only present a little bit more because I know time's going quickly is there was really a lot of excitement around new drugs that we have to treat very heavily relapsed Myeloma when most options are are already used up. They are coming into a new class of drug and probably the one that right now is generating the most interest are these drugs that are called bispecific antibodies.

Dr Joseph Mikhael: And to make it simple for patients, think of this drug as a drug that has two arms and when it's given to a patient, it grabs with one arm, the actual tumor itself, kind of like our monoclonal antibodies do; it grabs on and grabs tight on that tumor. But then with his other arm it grabs on to the T-cells of the patient. So these are like the soldier cells of the patient and it actually activates those T-cells with a nice good hand squeeze and tells that T-cell to come and help destroy the tumor. So it's a really a beautiful example of how we can employ the immune system. When we think of CAR-T cell therapy, which is of course another whole topic in and of itself, although there wasn't a lot of new data on CAR-T cell presented at ASCO, we'll see some later in the year. For CAR-T cells, you have to take T-cells out of a patient and train them to the tumor and then put them back into the patient.

Dr Joseph Mikhael: That can be very effective. But, but this is a way to almost bypass all of that and just go directly to hook the tumor to the T-cell and engage the T-cell. Now there's still some challenges with this drug there from side effects. The drug is given over a 28 day continuous infusion. It's not that easy. I think you had mentioned that Cindy Chmielewski was one of the people reporting she made what I thought was one of the funniest tweets I've ever seen about this. She said, well, if you're gonna give me a backpack for 28 days, it better be a cute backpack. Which I thought was funny, but the point being is that we're starting to see responses in patients and this drug is very active. We still need to work with it. This is not ready for the clinic yet, but those are the key abstracts that had me excited about the Myeloma world, knowing there's so many others, but knowing that we're making real progress here, my friend.

Gary: Well that sounds wonderful actually, what we're not going to do is I'm going to bypass my last question till later if in fact we have enough time. What do I like to do now is to go onto the other people on the panel and I'd ask them if they would just ask two questions apiece and we'll come back a little bit later after we've had an opportunity to talk to some of the listeners about what their questions are and then we'll come back again and finish off with our questions. So, and starting off. Let's go with Cindy.

Cynthia Chmielewski: Hi Dr. Joe. How you doing?

Dr Joseph Mikhael: I am doing fine my friend. I saw you for three seconds at ASCO and I am glad I got to see you right.

Cindy: Same here. Now let me see some of my questions. I guess the first one is, I'm going to ask you is like and I did attend a few sessions at ASCO this year on disparities and outcome to Myeloma patients and they were saying that patients will not be getting the same outcome, maybe geographic locations that are in close to a center of excellence where they socioeconomic status, types of insurance and so this kind of bothered me and I was wondering, is there any initiatives underway to address some of these disparities?

Dr Joseph Mikhael: So thanks for asking that question. And it is so absolutely fundamental. I mean we have seen this in other cancers and we've known about this myeloma in bits and pieces, but it's actually encouraging to me that there has been such an interest in understanding this that we can indeed reverse this problem that individuals who have less access to drugs and less access to transplant and have a certain socioeconomic status in the community. And frankly, our African American patients who, who have twice the incidence of Myeloma than Caucasian patients do not have the same outcomes. We've seen all this great progress in Myeloma in the last decade, but we've not seen it as fulfilled in the African American population. So that, to think like a doctor here, right, to cure a problem or to fix a problem, we need to know the problem.

Dr Joseph Mikhael: And thankfully there's been a lot of work, I've never seen more papers published and more meetings to discuss the disparity question in myeloma than in the last two years. And so that's encouraging to me. But in direct answer to your question, absolutely. There are multiple initiatives across the country. I have just launched a large initiative through the International Myeloma Foundation where we are doing a whole series of things in terms of reaching out to the African American community, leveraging the 150 support groups that we have across the country, recognizing that there are certain areas where there are greater concentrations of African American patients and patients with these disparities as you've described them, to better educate the community, to better educate the primary care doctors and the hematologist oncologist that are involved in their care. Trying to devise means to not only have physical centers of excellence but virtual centers of excellence so that individuals can get input and advice if they're not able to travel to a center of excellence or to an expert in the area.

Dr Joseph Mikhael: So, I have rarely seen a topic that has so impassioned many of us within the Myeloma community and I speak with a passionate heart when I say this is a problem that we want to address and I'm thankful that many steps are being taken in that vein. I should also mention that part of the way this will come to fruition of course as it will be a great partnership with a whole host of individuals. We've partnered with the Black Congressional Caucus, with individuals from industry, with individuals from the religious and social community. And so I'm very optimistic that we're going to start to see the gap filled and start to see things move in the right direction.

Cindy: Great. That's what I wanted to hear. You're so good at explaining how things work, could you talk about the drug selinexoR has a unique mechanism by the action, could you describe that a little bit and why is this drug potentially going to be valuable in myeloma therapy? And is there any inkling on what's happening with the FDA and FDA approval for selling it?

Dr Joseph Mikhael: Sure. Great. You always come up with great questions… All of yours come up with great questions. So it's ironic. I came from the lab this morning at TGen and we were discussing the mechanism of action of selinexoR. Now if I repeat what we said in the lab, you're thinking I'm speaking a different

language, so, so let me be more straightforward, let me put it this way. First of all, to have people understand the concept of the mechanism action. I often use this analogy, you know me and my analogy, so you're about to get two of them. I'm warning you. Spoiler alert, Dr Joe is going to give two analogies.

Dr Joseph Mikhael: So analogy number one is imagine that trying to take down myeloma is like trying to get into a house. Okay? And so naturally there's a front door and there's a back door and there may be a side door. So in the front door are proteasome inhibitors, and we know that we just keep going in that front door and we can get to the Myeloma. This is good, this is good. But eventually the Myeloma is smart enough and it says, you know what? We're going to lock the front door, we're going to barricade the front door and so we can't get in. So what you really want is another way to get into the building. You want a different mechanism of action. You want that back door as the immunomodulatory drugs or you want the side door like the monoclonal antibodies. But eventually, unfortunately this disease gets really smart and it starts blocking all the ways to come in so we can keep trying to get better ways to go through the front door, a stronger push through the front door.

Dr Joseph Mikhael: Yes, we have newer versions of old, of older and that helps to a certain extent, but we really wanted something different. We want to find a new window, like, hey look, there's a window over here. Let's go in through here. Or there's a side door here, there's a small door here or there's an attic here. There's a basement here. So the complexity of Myelomas, there's a hundred different ways to get into this building. Some of them are tiny holes, some of them are bigger. And we want to find those ones that let us get in. So SelinexoR is if you will, a new mechanism of action and it's treating the cell very differently than we did before. There's lots of ways to describe but my second analogy is, is what we have learned is that inside the nucleus of our cells, we have these good things that helps suppress tumors.

Dr Joseph Mikhael: We call them tumor suppressors and they are very good at trying to make sure that tumors don't damage the body. Again, I'm being very simple, but this is important. The problem is they leave the nucleus and they go off outside the nucleus. Sometimes they cycle back in, but they spend a lot of time leaving. And what we wish we could do is if only we could keep those tumor suppressors inside the nucleus. We could have the working for longer. So my analogy is you are hosting you and Gary and Priya are hosting a big party and everybody's coming to your party. But you know that there's some of those really cool people that as long as they stay at the party, everyone else was going to have a really good time.

Dr Joseph Mikhael: So once they arrive at the parties and then you close the doors that you don't let people leave. And I know that sounds really bad, I'm not trying to say you're imprisoning anybody, but the concept is that as long as you can keep those cool people at the party, everybody's having a good time. As long as we can keep those tumor suppressors inside the nucleus. And so this drug inhibit the export or stops the departure of these good tumor suppressors so that they stay inside the nucleus. I do think that this is an important drug because it is another mechanism of action. There have been some challenges with this drug in some of the side effects, but we're learning to overcome those in different ways. In fact, a group of us met to discuss this at length, just recently to find ways to develop best practices so that when this drug comes out, people know how to prevent the nausea or the lack of appetite that can sometimes carry through with this drug.

Dr Joseph Mikhael: I don't have any insider information and if I did I'd be careful to share anything. All I know is that this drug does have another assigned date in July where it'll be more formally reviewed by the FDA and we anticipate positivity. I do think, I think I can say honestly, I do think that this drug in the near future will be available to us. It might only be available and a fairly narrow area of people who have, if you will block the front door, the back door and the side door. People who have been exposed to and have had been resistant to monoclonal antibodies, proteasome inhibitors and immunomodulatory drugs. But I do think that will be its foot in the door because chances are we'll use it in combination later.

Cindy: Great. I love your analogy. Keep using them. Okay, thank you. I guess Matt's up next!

Gary: Yeah. I also had the same feeling about SelinexoR, like last just in had ASH in December. Everybody

was touting it and it was going to be the next best thing and then the FDA squashed it and it never even showed up on the radar for ASCO. So I was wondering is it dead or, or what's the situation? But it sounds what doctor, Dr Joe Mikhael has indicated is that there is hope for that drug because it sounded excellent. The only difference, the only reason it didn't make it as that there was one less representative on that panel who understood Myeloma.

Gary: Everybody else was kind of ignorant of it as in my opinion. I mean, not like a Myeloma specialist, if we had one more myeloma specialist on that panel, we would have had that drug already. But that's to be determined. Matt, it's your turn.

Matt Goldman: All right. Thanks Gary. Hi Dr. Joe, you've almost answered all my questions. I'll make this easy and just ask one which is with all the advances in treatment options and like you said, the use of monoclonal antibodies as a frontline drug. Is that changing how we're using transplants or have transplants are being done?

Dr Joseph Mikhael: I think you asked a very insightful question, Matt and if I were going through the whole ASCO review, I would have reviewed what for me was one of the most fascinating studies that was presented looking at can we actually avoid transplant and to make it simple, let me start my answer by saying right now, autologous stem cell transplant for patients who are eligible remains the standard of care. And I honestly don't think anything at ASCO has changed that. I still think it is the standard.

Dr Joseph Mikhael: I think on the other hand, if you discuss this with Myeloma experts, most of us will say it probably won't remain that way forever. We do think that whether it gets replaced with certain forms of CAR T cell therapy or just novel agents and then maybe that will be the case. But there was a very important study that was presented at ASCO by our Italian friends, a good friend of mine, Francesca Gay. And she presented a study which had three arms to it. But to keep it simple, I'll just speak about two arms. So patients were basically given a year of Carfilzomib, lenalidomide dexamethasone versus getting that plus the transplant and the intent was can a year of this kind of novel therapy be enough. What we had was the last year, two years ago, the French studies that showed to us that we had Bortezomib, lenalidomide Dex plus or minus transplant, there was still a benefit of transplant, although is the Bortezomib-len-Dex was only given for three months before transplant or eight months in total if you didn't get a transplant.

Dr Joseph Mikhael: So the question here is if we give Carfilzomib, which may be more potent and we give it for a full year, is that going to be enough? And initially it looked like that because the response rates were very similar and the depth of response was very similar in those patients. But what we found was that those patients that had not a transplant, so the non transplant group, their disease relapsed a little bit more quickly than those who had a transplant. So when you transplant, remember your intention is both depth of response and duration of response. So it's important to not just see the numbers go down but to stay down and it looks like the Krd where the Carfilzomib, lenalidomide, dex alone, although it gave you a very similar depths of response to the same group getting a transplant, it didn't keep you in remission for quite as long. And so right now, we still have to mull this over. The study is not finished. We've all been in trouble by overinterpreting early data, so we don't want to go overboard. But I think right now it's still sustains the notion that transplant still has a role met.

Matt: Okay. Thanks, and Gary that's all I have.

Gary: Well, thank you Matt. Very, very insightful question. Thank you so much. And now for the newbie, Dana Holmes, you're up.

Dana Holmes: Thanks. Thanks Gary. Hi Dr Joe. Your analogies are always so easy to understand and remember your buckets are spilling over analogy regarding smoldering was one of the first interviews I listened to when I was first diagnosed and I was hooked. So thank you for taking the time to break it down and make it so easy. Dr Joe, I believe a Mayo study a couple of years ago reported t(11;14) myeloma patients were not showing much benefit in overall survival as other myeloma subtypes we're in the age of

novel agents, suggesting that it might not be quite standard risk after all and prognosis may be inferior to what had long been, I guess thought of. So I'm going to cite three ASCO abstracts that seem to kind of now put us on the good side of the road. Dr Gasparetto had abstract 8032 using the myeloma connect registry, which suggests t(11;14) does not affect progression free survival or overall survival outcomes in newly diagnosed patients. The Hackensack group did E19 531 which concluded real world databases are useful in describing treatment patterns and outcomes and narrowly defined cohorts such as Myeloma with t(11;14) the overall survival results reported here is unexpectedly long and we'll be fully explored prior to presentation.

Dana: I missed the presentation of course. And then finally abstract 8015 which was an IMWG study reports t(11;14) patients receiving a combination of a PI+IMiD appear to have the best survival outcomes and those receiving an early stem cell transplant appear to have excellent survival with medium overall survival approaching 10 years. So can you comment please, especially in light of the fact that we may no longer now have Venetoclax in our toolbox, where do we, where do those patients with t(11;14) actually stand at this point?

Dr Joseph Mikhael: Wow, Dana. Wow. No, no. Honestly I just got, we just got this all the time. I joke sometimes Dana and say, you put 10 myeloma experts in a room and you have 12 opinions on this. I understand. I understand. I stand for sure. And that's why I'm glad you're asking this. I mean, the way that to back up for a quick sec and help the listeners appreciate this. You know, I often say the disease is called Multiple Myeloma for good cause. Meaning patients are very different with this disease. It really is multiple diseases in one. And one of the things we've actually identified is that the biology of the disease is really quite different. That lab meeting, I was discussed this morning that we in, we were looking at the vast different genetic changes that we have in this tumor.

Dr Joseph Mikhael: And we have some forms of myeloma that are really slow growing, some that are very fast growing, some that are sensitive to chemo, some that are insensitive to chemo. And we really almost have six different diseases in one. Translocation t(11;14) which just means that a little piece of chromosome 11 or a little piece of chromosome 14 that normally don't cohabitate are now cohabitating together. And that changes the effect on the cells of the tumor, is what we call Translocation t(11;14) and if we go way back, but some of the first work that was done almost 15 years ago by (not audible) and others, we saw that this was a distinct group of patients that their disease was a little bit different and it looks at the time that may be their long term outcomes were a little bit better than those who didn't have it or those who have different genetic abnormality.

Dr Joseph Mikhael: I think most of us believe that that still holds true. There have been a few blips along the way. As you mentioned, there was a Mayo study, there was another study that looked and maybe said, oh, maybe these individuals don't respond well to proteasome inhibitors. That's one of the reasons why the jury and the IMWG did this study. The problem is there's so much background noise, it's not incredibly common. I mean it is 15% of myeloma patients, but it's not all myeloma patients and there are lots of other variables. It's like saying to me, do Subaru drivers, when they're Subaru car is gray and they're driving on Thursdays, are they more likely get a speeding ticket then if they drive on Tuesday? A whole lot of variables depend on that, right? Maybe there's certain people that don't drive on Tuesdays and do drive on Thursdays.

Dr Joseph Mikhael: Maybe the traffic patterns are different. Maybe police officers are more likely to give out tickets on certain days. I mean I always, I explain this to patients because I say to them, yes there are genetic things, but this is one piece of the whole puzzle. Myeloma is so complicated that it's hard to say. So for any individual patient, we've all seen patients that have even the so called high risk cytogenetics, like the deletion 17 p or the translocation t(4;14) do extremely well. And then in other cases we've seen patients that don't have any of these high risk features and they sadly do very poorly. So it's always important to distinguish the sort of global patterns versus the individual patient. But in light of the studies that you quoted and I know them very well and we've had discussions around them.

Dr Joseph Mikhael: I think right now most of us believe that translocation t(11;14) is a little bit different

biologically. It has the potential if treated with even the drugs we have now appropriately for those patients to have a very long survival, perhaps longer than the average. My last comment would be, I know you mentioned that there are some challenges with Venetoclax. The FDA has put a hold on all clinical trials with Venetoclax right now in Myeloma as we review carefully what happened in that large study where unfortunately there were more patients into Veneta clacks the Velcade arm that died compared to those who are in the Velcade arm alone. I would say Dana, most of us believe in the Myeloma community that Venetoclax does have a role to play in Myeloma. Maybe it's only in the 11;14 patients. Maybe it's under certain precautions. We don't really know yet, but most of us feel that what happened is not a complete deal breaker because so many of us have seen patients truly benefit from the Venetoclax.

Dr Joseph Mikhael: So to put it all together, I would say most of us in the Myeloma community still feel that if given the appropriate treatment, patients with translocation 11;14, we'll do better than the average and that likely in some form we'll still have Venetoclax available and probably especially for that group.

Dana: Glad to hear all of the above. Certainly. My next question is specific to smoldering Myeloma and Dr Lonial's ECON trial in Atlanta. Lenalidomide versus observation alone in high risk smoldering patients? Was it intended from the outset of this trial to include smoldering patients who are intermediate risk or did the fact that the progression risk models you've evolved during the time of the trial closing intermediate risk patients to inadvertently be accrued for this trial? Looking now also at this new model of 20-2-20, which more aptly defines and differentiates high risk, intermediate and low risk, it's clear that the former model that they use in ECON trial really didn't. So how are we then able to actually interpret the outcomes of this trial if those with intermediate risk were inadvertently included in the data? Have the researchers actually teased out the intermediate risks from the high risk patients? I guess really how important is it to even do that? And I think I'm so fixated on this because of the excitement that I'm hearing and feeling over the results which may lead to change in practice. Dr. Joe. I use myself as an example. I was diagnosed back in early 2012 and I met the criteria for this particular clinical trial. However, I didn't enroll. I haven't been treated and I remained stable seven years out. But how'd I enrolled and received Revlimid and even just remain stable on it, it would have been reported. It was the Revlimid which kept me from progressing. So, in light of this, I'm being cautious as to how I'm looking at these results, especially as I just viewed a video this morning, a presentation that Dr Raja gave, I guess at ASCO where she stated that there was a doubling of secondary malignant cancers in the treatment arm of this particular trial. What are your thoughts on that?

Dr Joseph Mikhael: Yeah. Again, Dana a very, very insightful and complex question. I'm conscious of time, but I want to answer this and I want to answer it very carefully because this is so absolutely important. It is very different when we say, Oh look, we've developed a new drug that we can add onto a regimen, or we've developed a new class of drugs that is going to be used in patients that are very heavily pretreated. That is massively different than potentially saying that we are going to treat basically,well, patients with a drug. The bar has to be so much higher because the potential for risk is massive. It's like saying 5% of the adult population probably has some form of MGUS. I am not going to treat 5% of this planet. I mean we have to be careful because if the treatment, no matter what the treatment is, everything comes with risk.

Dr Joseph Mikhael: Right? As I sometimes say, unless its mother's milk, everything comes with real risks for the very first patient ever treated on the thalidomide, smoldering myeloma study tragically died six weeks after starting of a massive blood clot in the lungs. And it was a reminder to us that the most sacred adage we have in medicine is above all do no harm. Now that has to be balanced, right? Everyone on this call is at some point going to get onto the highway probably in the next week or so. And we know there's a risk of getting it when you drive and when you see. So we all accept some degree of risk. Now with that as the background, I do not think that this study is practice changing. And I'm in the camp of people which is I believe still the majority of myeloma physicians and treaters and providers who feel that there are big issues with both this study in the Spanish study.

Dr Joseph Mikhael: And I disagree with Dr Lonial that we are immediately treating all high risk smoldering Myeloma for a lot of reasons. One, because just as you've said, as the lines change, of course, and it's understandable definitions, the criteria is it has to catch up and this isn't reflecting what we think of the new

biology of the disease. Secondly, although the drug did prevent or at least delay, we have to distinguish delay versus prevent. Some of the great work we're doing at the IMF in Myeloma working group is yes, I mean who wouldn't want to prevent the disease? But do I really believe, although it's a fantastic drug, do I really think lenalidomide alone is actually going to prevent myeloma? Absolutely not. I think there's a lot more to the immune system than just doing that. And then as you've said, there are as always certain toxicities.

Dr Joseph Mikhael: I'm going to accept a slight increase in second cancers in a patient who already has a defined cancer that's needed treatment and as it were, the devil, you know, versus the devil you don't, I mean I'm hesitant to not give someone a drug I know is gonna make them live longer because they have a 1 or 2% chance of developing something new. But when it's a patient who is asymptomatic, who doesn't yet have an active disease, granted it was 50% higher. It was about 2.5 – 4.5%. So the absolute difference was about 2 or 2 1/4 %. It's not a huge %, but it adds up. And the last point I'll make is that unfortunately 51% of patients on that study had to come off the drug. So this is not the ideal strategy for high risk disease.

Dr Joseph Mikhael: Yes. The drug is very well tolerated in general that people who are really well, they don't want any effect on their quality of life. And so the fact that half the patients couldn't stay on the drug for the intended period. Now Dr Lonial's response when I asked him that question was, well, maybe they don't need it as long as we anticipated they needed it. And that's a very good point and we need to examine it. But I think there's still enough unanswered questions that right now the strategy of saying let's better define smoldering Myeloma so we know what needs really to be treated and if you're going to treat myeloma, we treat it fully. We don't have treated with lenalidomide alone. We're starting to draw lines close to the cliff and say if you cross this line, we're going to treat you as if you were falling down the cliff because you're just so close. I think many of us almost feel that we might have smoldering myeloma disappear from a deputy and then just say everything most certain point is basically MGUS everything after that is Active Myeloma.

Dr Joseph Mikhael: For advanced? We're not there yet. We're moving forward.

Dana: Yeah. I think the excitement needs to be tempered a bit because I think it could do a lot more damage than good especially within the community oncology group who may not really be putting a lot of thought into it and just throwing their patients onto Rev and Dex. So I'm glad that we addressed this. Thank you.

Dr Joseph Mikhael: You sound just like I did after the abstract. I don't ever want to temper people's excitement about research. This is what we do and this is wonderful, but I am clearly not telling anybody to run out to their oncologist and get smoldering Myeloma treated right away. I do not think that is wise and I share your conservative approach.

Dana: I do think however, that there are two arguments to be made though still about whether it's good enough to just control the disease for the rest of my life or just to knock it out of the park. I mean, if I could be guaranteed that I could have it controlled for the rest of my life and live a decent quality of life, then that's an option, taking the risks into consideration. But I think that these questions have not been answered yet.

Dr Joseph Mikhael: And I think in the broader picture for the audience, I know we're going to turn to other questions momentarily, but that is a really important principle in general, right? People ask me all the time, when are we going to cure myeloma and Myeloma is complicated. It's like saying, why don't we get a fix the economy, it's not one thing that'll change the economy tomorrow. There's lots of things that go into it and so we don't cure high blood pressure or diabetes. We control it in the long term. We may have to go down more of process controlling. Obviously we'd like to cure, which basically means it gives someone a defined period of time of treatment and then they don't need any more treatment. We're not there yet, so we're definitely getting closer to it with these great combinations we've developed.

Gary: Thank you very much. Dana, you done a great job. What I like to do is to turn it over to Priya and if you could bring up the callers on the line anyway, if we get through all of those, we will go back round with

additional questions from the panel.

Priya: Yes. Listeners if you have a question for Dr Joe, please dial in using (718) 664-6574. We have a caller on, Bonnie is here, who wants to ask a question. Bonnie, you're on air, please ask your question.

Bonnie: Hi Dr. Joe, thanks so much for your time. I have questions that are around the topic of stem cell transplants. I watched Dr Raje's presentation of Dr. Gay's study and she pointed out at the maintenance randomization ended up sort of (not audible) in my opinion, being able to draw a conclusion about the advanced stem cells transplant.

Dr Joseph Mikhael: This is sort of a traditional challenge that we always have in myeloma, which is sometimes would you see results in a study, it's not just a function of what's happening in the study, it's happening, it's a function of what happens after the study. So in the study that I described, patients get carfilzomib, lenalidomide, dexamethasone basically plus or minus a transplant, and then they continue that. And then, but there was a so called second randomization where patients either continued on carfilzomib and lenalidomide or just lenalidomide, and it's still too early to know if we know that it's still , too early to know if that second randomization and the paths that people took later may have influenced the comments I made earlier about relapsing sooner.

Dr Joseph Mikhael: Either way it is, it still speaks to the power of transplants earlier on, but it may also speak to the weakness or the power of that second randomization, which is why we do that so that we can see, it's not just about one step, it's about a second step in the disease. So I think that, the jury is still out on this as a word still a little bit early to draw that conclusion. Comment from Dr. Raja is very insightful, which points to the fact that as I said earlier, we need longer follow up of these studies. We've all been led astray, right? As I sometimes say, going back to my analogy, you want to predict the end of the super bowl at halftime or even after the third quarter. That doesn't always work right? There have a lot of Super Bowls that have been determined at the very end. And so these studies, although we allow them to be presented at earlier points in their treatment so that we can detect early trends, either positive or negative, we need to wait a little bit longer to understand that.

Bonnie: Yes, thank you. I understand that. And, and just clarify one thing for me, tell me if my thinking is on track here. I mean all over the Internet patients are constantly asking, should I go on maintenance or should I have a stem cell transplant? Then everybody presents their arguments back and forth. But they should have one background assumption that I want to check with you and that is that we're assuming that people have the option to do as the late transplants if it doesn't all work out, with the novel agents upfront. But like this study, the Forte child, it's only from pairing novel agents versus an upfront transplant, but doesn't clarify whether or not it is wise to wait for a delayed transplant for certain patients because they may not have that option down the road.

Dr Joseph Mikhael: Correct. It's not just a reality that no one study can answer all of those questions. Which is why some of them, we end up having to they day, there's only so much you can gain from each study. But we learned a little bit more about that from the French study, the IFM study where patients who didn't have a transplant in the transplant arm, but when they relapsed, they were allowed to go to transplant the course and at 80% of them are 79% of them had a transplant at first relapse. So we knew it was feasible. So many people look at that study and say, Oh, well we could do it a second transplant or do sorry, delay the transplant, delayed transplant. This study is designed to answer that question. But I think it's an important discussion to have with patients. I think it's reasonable to delay a transplant if there are certain conditions that are met, but usually not beyond the first relapse. We really should plan to give it at first relapse.

Bonnie: Okay. Thank you. Thank you so much. Thank you.

Priya: Dr Mikhael, we have couple of questions posted on the page, the place where people are listening to. Let me just quickly go over those. One of them says what are the most promising drugs forthcoming to treat multiple Myeloma for those of us who have had numerous lines of treatment, what are the best ways for

patients to stay as healthy as possible then as long as possible?

Dr Joseph Mikhael: So both are great questions, of course, I mean the most promising dru