ASH 2019 Annual Meeting Multiple Myeloma Updates

The 62nd ASH (American Society of Hematology) annual meeting was held in early December 2019. We are talking to Dr Shaji Kumar about new research presented at ASH, including disease-specific treatment updates on multiple myeloma, the role of precision medicine & clinical trials discussed at the world's most comprehensive hematology event of the year.

Full Transcript:

Shweta Mishra: Good evening and welcome to Curetalks. This is Shweta Mishra, your host, and I wish you all a very happy new year on behalf of the Cure talks team today. We are kicking off the New Year 2020 with a discussion with Dr. Shaji Kumar, Professor of Medicine at the Mayo Clinic College of Medicine and a consultant at the Mayo Clinic Division of Hematology to learn about new treatment and research updates on multiple myeloma that were presented at the American Society of Hematology annual meeting held in December 2019. I welcome you to Curetalks, Dr. Kumar.

Dr Shaji Kumar: Thank you Shweta. Good to be here.

Shweta: Pleasure is all ours Dr Kumar. On the panel, we have our very knowledgeable myeloma patient advocates Gary Peterson, Jack Aiello and Cynthia Chmielewski. Welcome to the show Gary, Jack and Cindy. Thanks for being here today. We will be discussing questions sent in via email in the last few minutes of the show. So people listening in to the talk can send their questions to shweta@trialx.com or post them on the page where you're listening to the show right now. So without further delay, I will now hand it over to our co host, Gary Peterson to lead the panel today with Dr Shaji Kumar. Gary, please take over.

Gary Petersen: Okay, well, thank you very much. And thanks for all the things that you folks provide for patient education. And Dr. Kumar, welcome to the program. You have an excellent background and you're obviously part of the Dream Team at Mayo Clinic. You've got so many great doctors and you are absolutely one of them. So thank you. He's the professor of medicine, Mayo Clinic College of Medicine, consultant, division of Hematology and medical director, Cancer Clinic Research Office, Mayo Clinic, Rochester, Minnesota. And his research team evaluates the in vitro activity of novel drugs that are based on the mechanism of action and are unlikely to have activity in the setting of myeloma. Promising drugs are brought onto the clinic through early stage clinical trials and phase one and two studies. And I can't tell you how important those are and that we brought so many in the last 10 years to fruition through the efforts of Dr. Kumar and many others. So, without those drugs, we wouldn't live nearly as long as myeloma patients. I want to say there's so many other things, I could go on and on and on, but I don't want to spend the time to spend discussing ASH and all the things that Dr. Kumar finds to be important to the patient and to the myeloma community at large. But one thing I can't bypass is the work that he and other US myeloma patients have made. He, Noopor Raje, and Sundar Jagannath are several as well from India that provided a template for treatment in India. We have a template from the folks at Mayo call mSMART, which I think is very, very important provides knowledge on how to treat myeloma patients for anybody even in the clinical setting, not necessarily educational institute in the US, so it's called the consensus and management of multiple myeloma in Indian and I think it's a banner ever done is everybody's part. So thank you very much for that.

Gary: Now my first question is going to be kind of the one that will just give us a little summary. I look at the program that we saw at ASH and there are so many new and important developments there. Many of them are just brand new classes of drugs CAR-T, that's a new class BiTE is a new class, Antibody drug conjugate is a new class of CLR, which is another conjugate but it's a nuclear conjugate. There's so many of those. Could you provide insights and what you feel the highlights and the major takeaways that you had from the

conference?

Dr Shaji Kumar: Sure. Thank you, Gary, for the opportunity. So I think as with every year, the 2019 was quite an exciting meeting from a myeloma perspective. We saw a lot of new data as well as longer term follow up on previously present data confirming the origin of findings. I think when you look at how myeloma has changed over the past, especially the past few years. It's really interesting to see that now we are starting to look at some overall concepts about how you manage patients, should patients with smoldering myeloma be treated, should we be using combinations, where should the combinations be used, what drugs make good combinations, can we stop treatment in some of these patients, or define what is the ideal duration of treatment?

Dr Shaji Kumar: So I think we are at a point where we have enough tools in our hands to start asking some of the fundamental questions that dictate how patients are treated. That is a big difference from maybe five, maybe even five years ago when he was still trying to figure out which drugs work better. Obviously, we still need to find new drugs. And as you already mentioned, there have been several new drugs and drug classes that we saw some early data at the ASH. But I think, for me, some of them in addition to those very important aspects of the meeting, were the clinical trials that are looking at the candidate paradigm of treating myeloma.

Dr Shaji Kumar: So, as we go through, we will touch upon many of these specific agents. But I think some of the things that are really exciting, I think, obviously, the immunotherapy approaches. So we clearly have been looking at the data from all the CAR-T trials for the past few years. Now we have more of what we call the T-cell engagers or bi-specific T-cell engagers. And we saw some data with a brand new molecule from Celgene at the meeting that looked quite promising in terms of the proportion of patients who responded. We also saw data with some non immune therapies, for example, the CLR 131. We saw data from Selinexor which is now approved, but we saw the data in combination with other agents like Pomalidomide. There was some early data with Melflufen and that is going through clinical trials. It's a different type of alkylator.

Dr Shaji Kumar: And one might wonder why we should be bothering about alkylators. I think it's important because as a drug class it still is quite active. And lots of patients don't actually get treated with alkylating agents in the first few lines of therapy, so that class actually becomes quite important when some of these new drugs have stopped working.

Gary: Is it a targeted approach?

Dr Shaji Kumar: Melphalan, it's not targeting in the true sense, it's just the way it is metabolized, they feel that you probably have a higher concentration of the drugs within these cancer cells. So it's in a way, it's supposed to make it more tumor specific but not to the same degree as what we would think about it antibodies or some of those things.

Gary: Thank you. I didn't mean to interrupt. I'm sorry. Okay, so with that, what I'll do is we've got Jack Aiello, who is going to be leaving us in 20 minutes. So, what we'd like to do is to have Jack ask his questions first, then I'll follow the rest of mine and then Cindy, if that's alright with you, All right, Jack, are you online?

Jack Aiello: I am and thanks, Gary for accommodating my schedule. And Dr. Kumar it's always nice talking with you. I hope you're staying warm. I had three questions. Recently, there's been a lot of data presented from trials for high risk smoldering myeloma patients and the data, the trials are focusing on delaying progression to myeloma or possibly even curing patients at this stage. So outside of trials, do you personally treat high risk smoldering myeloma patients today? And if so, how?

Dr Shaji Kumar: Jack, I think this is probably the kind of the most hotly debated topic in myeloma right now. I'm glad you brought it up. I think in order to answer your question, I think and what I'm going to do is just briefly touch upon the data that kind of guides what I do in the clinic. So in order to do any kind of, we know

that patients with smoldering myeloma has a very high risk of progressing to myeloma, we're talking about roughly half of the patients progressing in the first five years and maybe another third in the overall, two thirds of the patients in the first 10 years. Now the first requirement to be able to intervene early is to identify the people who are the highest risk of progression. We had some models from the past, which no longer really works the way they were originally designed to, because we have changed the definition of myeloma and smoldering myeloma.

Dr Shaji Kumar: So recently, the International myeloma working group did a large study with about 1300 patients with smoldering myeloma where we looked at various risk factors and developed a new model, which essentially validates something that we had developed at the Mayo Clinic, what we call the 20 to 20 model. And this seems to be fairly sensitive and specific in terms of identifying patients who are at the highest risk of progression. So one, we have a tool that is better than what we had before in identifying the high risk patients. Now, the second important thing is obviously clinical trials demonstrating that the earlier intervention when actually helps patients live longer. And importantly does not interfere or make subsequent treatments less effective. So there are two big trials that can be used to guide our treatment approach.

Dr Shaji Kumar: The first one was the QUIREDEX trial from the Spanish group where they randomized patients to getting lenalidomide dexamethasone or observation in patients with high risk smoldering myeloma. That study showed that there was a progression free survival advantage, but more importantly, also an improved overall survival by treating high risk patients earlier. Even more importantly, that trial showed that the impact of the subsequent treatments after the lenalidomide and dexamethasone stops working, is not adult impacted by this early intervention strategy. So this disadvantage of the trial of why the trial has not really been that adopted universally into practice, is because the way they define high risk is not something that all of us can do, and two, they did not use advanced imaging techniques for that trial. So some of those, about a third of the patients who were enrolled, would today be called myeloma and not just smoldering myeloma.

Dr Shaji Kumar: So that's where the recent ECOG trial that Dr. Sagal Lonial presented, or published recently, where patients with smoldering myeloma were randomized where they are getting lenalidomide alone or observation. And he showed that patients who are considered to be high risk by the new Mayo 20-20-20 system, or 20-2-20 system really seem to benefit by the early treatment with lenalidomide. So now we have two trials showing that there is a benefit for early intervention. And this certainly does not appear to be a significant, a potential for harm at this point. So how do we use that data in the practice. So what I do is actually go over the data with the patient and in simple terms, to say what benefits we are looking at by trying to start some treatment with the goal of delaying the progression to myeloma.

Dr Shaji Kumar: So what the choices that we kind of present is one, we could do what the clinical trials did, which is to treat with lenalidomide-dexamethasone. Two, we can consider a clinical trial that's currently open for high risk smoldering. And all the trials currently are either phase two trials with single arm or randomized trials that are looking at two different treatment approaches. So observation is no longer considered to be a control arm in this trial. The third option, I think it's obviously open to the patient is that maybe we'll just continue to watch. But if we do do that, I think it's important to keep an extremely close watch on what's happening with these patients. So you kind of alluded to the curative approaches and I think that is kind of a separate line of investigation so to speak, because we all hypothesized that if we catch myeloma in the smoldering phase, maybe the disease is not that complex, and we can potentially may have a better chance to eradicate those cells completely.

Dr Shaji Kumar: So there are trials looking at trying to 'cure' smoldering myeloma. One of them was the CESAR trial that Dr. Mateos from Spain is doing where she's treating them with Carfilzomib, lenalidomide, dexamethasone and a stem cell transplant. We have a trial called ASCENT Trial in the US where we are treating patients with Carfilzomib, lenalidomide, daratumumab and dexamethasone, now soon to be expanded to include transplant also. And the goal here is to give a short duration of intense therapy to see if we can wipe out those bad cells completely. So, I think where we are moving forward is, the next question that you need to answer is, if we do find smoldering myeloma early, or if you identify higher smoldering

myeloma, do we just give them one drug to delay progression or do we give them three drug combinations like myeloma and treat them like myeloma, or with even more intense approach to try and cure them.

Jack: Thank you very much for that information. My second question is specifically from a patient who has deletion 17p. And he asked me if there were any new insights at ASH on treating either newly diagnosed or relapse refractory patients that are considered high-risk with deletion 17p and I didn't remember any so I thought I would ask you.

Dr Shaji Kumar: Absolutely. I think another very important area is the management of high risk myeloma, 17p deletion being one of the highest risk groups. So what we know is that all the treatments that have come along, that significantly made a difference for the standard risk. So that's three quarters of the patients. And for the other one quarter of the patients, the benefit has not been that dramatic. It's better than before, but not quite as much as the standard. So the question is how do we deal with this differently? The best clue that we have for a different approach are some of the data from previous studies and those presented at ASH showing that if you become minimal residual disease negative and you are high risk, you have the highest probability of long term survival. Now, what these studies don't tell us is whether getting to be MRD negative with a given treatment is more because of the underlying disease characteristic or is it something to do with the treatment we gave them.

Dr Shaji Kumar: Nevertheless, I think the high risk patients ask one group of patients where I think we can, kind of extrapolate the data we have and say, yes, we want to try and get these patients to have minimal residual disease negative state, by using if one combination doesn't work, maybe more intense therapy or a different combination might be the approach to take, but somehow we want to get them to a minimal residual disease negative state. Now, this kind of approach of using either minimal residual disease negativity as a target or using specific drugs like bortezomib in patients with 4;14 translocation or deletion of 17p or using tandem autologous stem cell transplant in patients with deletion 17p. All of this appears to have some benefit. They don't really go into the biology of the disease, specific changes in the myeloma cell. So they are aimed at leaving behind as few cells as possible so the chances of further mutations are reduced.

Dr Shaji Kumar: But there are also approaches trying to understand why a given patient high-risk and can we specifically go after that. And to this end, there are some drugs that are specifically targeting, for example, the cells that are deleted in 17p, we also have the MyDRUG trial that is ongoing right now, which will be doing genomic sequencing and look at in high risk patients and look at what mutations they have and try to use drugs that are specifically targeted to that mutation. So, it's still a work in progress, but I think what we can do today is trying to treat them to the deepest response possible.

Jack: Got it. Thank you. And you brought up MRD minimum or measurable residual disease, which I know has been shown to have prognostic value, but do you use it yourself to help guide treatment decisions?

Dr Shaji Kumar: Yeah, to some extent, and I think as you already pointed out, if you take 100 patients getting the same treatment, and let's say 50 of them became minimal residual disease negative, then those patients clearly will do better than the 50 who did not get to be minimal residual disease negative. And just to frame reference, the way we define MRD negativity is that we should be able to use the test that can detect 1 in 100,000 cells. So if you have a hundred thousand cells and you have one myeloma cell, we should be able to identify it. And we can do that by flow cytometry or by using something called the next generation sequencing. So but what don't know is that the 50 people who did not get MRD negativity, if we gave them a different treatment, and try to push them to be MRD negative will it make a difference for them.

Dr Shaji Kumar: So that data is lacking right now from effective clinical trials. So we all old talk about how MRD testing is a prognostic tool, and not an actionable tool. So there are phase three trials ongoing that are asking this specific question. At the end of maintenance treatment, if you're still MRD positive, should we make the maintenance treatment more intense? Or if you are getting maintenance for a couple of years and you are MRD negative, can you stop it? So those are ongoing right now and trials are looking at if you are MRD positive can we add a fourth drug, would it be beneficial? But in the high-risk patients as we just talked

about, I don't think we have the luxury of waiting for this phase three trials to read out. I think for those people, I think we can already, I think putting on the side of caution or to be more proactive for those patients, I think we can implement that as a clinical tool.

Jack: And just to clarify for patients listening, you mentioned 10 to the fifth or 10 of the six. But you also use imaging test to determine if someone's MRD negative?

Dr Shaji Kumar: Right, that is very correct. In fact, the International Myeloma Working Group response criteria says you can be born marrow MRD negative, but to be truly called MRD negative, we also want to be doing a PET scan to make sure there is no myeloma outside of the bone marrow. It has not been uniformly implemented in all clinical trials right now. We are just basing most of the readout on looking at the bone marrow MRD only, but I think especially in the high risk patients, it's important to look outside because many of those patients actually do get extra medullary disease.

Jack: Thanks so much, Dr. Kumar. And I look forward to the next time I see you.

Gary: Thank you, Jack. So I'll finish up my questions, one of which is CAR-T has had great expectations with cures and leukemia. And we kind of waited with bated breath for the same kind of results for myeloma, but we didn't see that. So, I know that the CAR-T is being improved, but do you see any that may lead to a cure or extended survival?

Dr Shaji Kumar: I know that there's this mixed feelings about what the CAR-T trials have shown so far. But I think a lot of it is a reflection of, you put so much hope on to that particular modality. And I'm really not surprised by the results that we have seen so far, for two reasons. One, all the CAR-T drugs have been done in the setting of myeloma that has become refractory or not responding anymore to any of the drugs. So it's really kind of a last ditch attempt, so to speak, which I don't think reflects the true potential of that modality. And the second thing is even if it is really the way we thought it would be in terms of its efficacy, we know that the myeloma cells continuously mutate and get new genetic abnormalities. So it's quite possible that it's not going to be the way to control disease long term for every patient.

Dr Shaji Kumar: Maybe there is a subset of patients who might have the maximum impact from the CAR-T trials or the CAR-T cell approach. So I think what the ASH data kind of give us a little bit of a clue. So there was data presented the long term data from the Chinese trial, where they saw progression free survival, up to like 27-28 months in patients who were only refractory to bortezomib and thalidomide which would be like an earlier stage of relapse, even though they have received these drugs multiple times. So I think the key is to see one, which patients would benefit the most, and what stage of the disease would the treatment with CAR-T be the most appropriate? Would it be best after just four cycles of induction therapy or in place of transplant? Would it be a way to get rid of the minimal residual disease after a transplant or should be using it in the setting of the first relapse? So those are the trials that are currently ongoing, so we certainly will be getting more information That.

Gary: All right, well, thank you very much. Well, one thing, it's kind of interesting, I think along those lines is you say that the progression free survival is something like eight or nine months. But when you look at daratumumab, its progression free survival was 1.7 months. At one point at the very beginning, and now it's like this, everything goes better with Dara. And I really feel that ICER at that, it's a well 1.7 months, it's not $150,000 a year. But when you look at what it does, it's amazing how well it is. And not only that, Selinexor was I think 3.5 months and CRL 131 is like 5.9 months, and now you're talking about eight or nine. Now if you move that further in, like you said are further up closer to diagnosis, maybe, maybe there's a cure there someplace but yeah, it's…

Dr Shaji Kumar: I don't think we ever seen what CAR-T cells can do. So I think we just need to stay tuned.

Gary: okay, now there's antibody drug conjugates there's BiTE, there's BCMA targeted therapies,selinexor, melflufen, CRL 131 and so many others, which have you got your eye on for the road to

a cure?

Dr Shaji Kumar: Right. I mean, to me, the best message from the CAR-T trials is that immunotherapy actually worked and immunotherapy using , modifying the T-cells, which obviously, people have been working on for three or four decades now clearly shows promise. The fact that you can have somebody with rip roaring myeloma, and two months later, you have no myeloma so detectable is really powerful in terms of the efficacy of the platform. So I think immunotherapy is going to be a very, very important part of myeloma treatment going forward. So now which immunotherapy is going to be the, is it going to be the autologous CAR-T cells, which has the disadvantage of having to collect the patient cells wait for a while before giving it back? Or do we do something like an allogeneic CAR-T cells which is basically off the shelf copy that you can use for even better not even use a cell at all, but use something like a BiTE which essentially kind of without modifying the T-cells kind of tracks the T-cells kicking and screaming to the myeloma cells so they can actually do the work.

Dr Shaji Kumar: To me the BiTE's really has two advantages. One, it can be scaled up rapidly; you can treat a lot of patients without having to wait. And second, you can keep repeating it. And that's the platform that you can use by first one time we may use BCMA. Next time, it could be a BiTE against some other antigen. Third time, it could be a BiTE against a third different antigen. And so there's a lot more potential in terms of just making it available to a larger number of patients, then CAR-T cells might be amenable too. So I think I would if I were to place my bet on all these different things that we saw, I certainly think the BiTE is something that we really want to keep an eye on.

Gary: Okay, thank you very much. Now, we'll go to Cindy for her question. Cindy, are you there? All right, you can answer your first question which I see, by the way happens to be an 11 part question.

Cythia Chmielewski: All related. So thank you for taking the time to answer our questions, even though they may be 11 part questions. My first one is going back to the CAR-T cells, but now that we're seeing them more and more in myeloma, I now start hearing people saying, well, all these T cells aren't like, right now really have what's called the battle of the CAR-T cell and someday we're going to have this for worry for myeloma. So can you elaborate a little bit about that? Like what is meant by the construct of the CAR-T cells? What are binding sites, turn on turn off switches? How are all these CAR-T cells alike, how are they different? And how, as a myeloma patient with so many CAR-T cells available, how can I go out and make my choice as which trial I might want to be part of?

Dr Shaji Kumar: I like a good analogy about the Model T and the Ferrari. Clearly, we are at the very early stages of development and you already seen in the past few years, much in terms of refinement of the platform. So, kind of starting off with their questions, what is it? What does what happens to the CAR-T cells, so, right, so, you're essentially taking a T-cell receptor which is what the T-cell uses to identify the tumor cells and basically modifying it to attach itself to or seek a particular antigen that's on the myeloma cell. So, the most common thing that has been used is what we call the BCMA or the B cell maturation antigen. So, the receptor is obviously, we create the receptor and using a virus, you basically insert the DNA that will encode for the receptor into the T cells. And basically, once that DNA is inserted through the virus into the T cell, then these T cells will start expressing that receptor that was artificially created or put together and once they express that, then they are able to identify the tumor cells much more efficiently and then bind to them.

Dr Shaji Kumar: There are some of these CAR-T cells, especially the allogeneic CAR-T cells where they might be what they call a kind of a self destruction or self destruct mechanism where if something were to go out of control, we can essentially turn off these T cells that make them, kind of killing them. But I think what is happening, the three or four different ways, I think the CAR-T cells can be improved and that are ongoing right now. So, one of them is looking at these receptors that can identify more than one protein at a time in order to allow it to bind more efficiently to the tumor cells. Second one is trying to use CAR-T cells in combination. So, two different CAR-T cells targeting different proteins can be used in combination, trying to use non viral methods to artificially modify the T cells. One of the disadvantages of using a virus is that there is the risk of other DNA damage.

Dr Shaji Kumar: So the FDA, for example, would want these patients to be followed for up to 15 years after they get these. So that is a burden, in terms of follow up. So there are new methodologies that are being developed where you don't need to depend on a virus, which then means that we may not have to watch or follow patients for that long. Now, there are other methods where the way these T-cells are cultured or expanded, they are looking at adding some drug to one, to make those cells mature faster so that people don't have to wait too long. Secondly is to see if we can change the composition of the CAR-T cell graft so that we have more of what we call memory type T cells that can live longer. Then there are approaches trying to see if we can actually make the tumor cells express this protein at a higher density than what it typically does, so that they become kind of more juicier targets for these T-cells.

Dr Shaji Kumar: Then, as I said we are trying to use combination for the types of CAR-T cells either together or one after the other. And then there are ways to try and see if we can actually, if people are not getting to be MRD negative after the CAR-T cell can be reinfused the CAR-T cells. So again, and then finally, there are also studies looking to see if we can use other medications like checkpoint inhibitors to try and can wake up these T-Cells after they've kind of gone to sleep.

Cindy: Whoa, wow. So there's a lot going on.

Dr Shaji Kumar: There is a lot going on and it is really hard for somebody to choose right now. The thing is that all clinical trials, so I think there's not much you can differentiate between them. But once one of them gets approved, then obviously, that is something that would be a default.

Cindy: Exactly. And one could build on the other and what you learn in what style you can apply to the next. So yes, this is very exciting. Great. My next question is about the QP mass spectrometry. I'm not even sure how you say it. And is that how you say it?

Dr Shaji Kumar: Yeah, it just various different names. So yeah.

Cindy: And what it's role in monitoring myeloma, is it readily available? What advantages does it have over the current SPEP method? And do you think this will be changing in the near future?

Dr Shaji Kumar: Right. So I think the whole platform is using mass spectrometry is going to really revolutionize how we assess the disease response, and maybe even making diagnosis of certain rarer conditions like amyloidosis, and so forth. So for everyone on the phone, who are not familiar with this technology, what it does is it essentially breaks up the protein into small tiny pieces and look at the sequence of the amino acids that make up the protein and then do a matching to see which protein does it resemble. And you think that way we can identify extremely small amounts of the monoclonal protein. So, the goal is in the future, that we would be able to replace the serum protein electrophoresis and immunofixation by using this methodology.

Dr Shaji Kumar: So the Mayo Clinic already the lab has switched from the immunofixation to using mass spec, we call it the mass fix, and it is almost tenfold more sensitive than the immuno fixation in identifying trace amounts of monoclonal protein. So, what the Spanish group presented in the context of this research trial at ASH is just a variation of the same, the underlying platform is the same instead of using a more specific way we can detect extremely small amounts of monoclonal protein. So, the question is going to be, how does this help us detect minimal residual disease, does it replace the bone marrow, does it add on to the bone marrow, those are the cities that are currently ongoing.

Cindy: Okay, and is mass spectrometry done on your blood or on your bone marrow?

Dr Shaji Kumar: The mass spectrometry is done in the blood.

Cindy: So that's what makes it nice. You'll not have to have as many bone marrow biopsies.

Dr Shaji Kumar: Exactly. I mean, we don't have the evidence to say that it can replace the bone marrow yet, but I mean, that is our eventual goal.

Cindy: Okay, great. Now, what I'm hearing more about is this 1q21 game. I really hadn't heard about that too much in the past. Is this something that's new, a new product, not a sticker? Is it something I just never heard of? Can you talk a little bit about that?

Dr Shaji Kumar: Absolutely. So basically what happens is this amplification of a portion of the kind of what we call the long arm of chromosome one is the region is called 21. So that area of the chromosome has several genes that we think are important for myeloma biology. And what happens sometimes these patients can have one to several copies of the same thing duplicated over and over again. And what we have seen is anywhere from 15 to 40% of patients could have 1q amplification that you can detect on a FISH. And it varies depending upon the patient population is steady. In the newly diagnosed patients we are probably talking about maybe 15 to 20%.

Dr Shaji Kumar: In the relapse patients, it could be as high as 50 to 60% of the patients. So this is an abnormality that is unlike a translocation 4;14 is not present, then the myeloma cells originally start, but over time it starts accumulating them. And the more of this they accumulate, the more aggressive the myeloma behavior becomes. This is in addition to the previously described abnormalities that represent a high risk abnormality.

Cindy: Okay, I just I guess I never heard of that before. So that was something I was curious about. And what about Venetoclax? Is there a role for that in myeloma, or do you think it's just going to be used in some of the other cancers?

Dr Shaji Kumar: No, I think Venetoclax is going to have a significant role in treating myeloma. So, there were a couple of very interesting follow up studies from the Bellini trial that was presented at ASH. So there are two things we know. One is if you have a translocation 11; 14 two-thirds of the patients will respond to just Venetoclax and dexamethasone without any of the other drugs. Now, if you don't have the 11;14 translocation, but if you have a high level for the Bcl-2 protein, then patients will respond to the Venetoclax used in combination with other drugs. So the Bellini trial was used in combination with bortezomib and over 80% of those patients responded to the treatment.

Dr Shaji Kumar: The problem with that phase three trial was that we also saw some increase that happened in the Venetoclax arm. And as we started dissecting the data, what was clear was that the patients who were cured by the trial, were people who had high risk myeloma and the ones with low Bcl-2 and did not have 11; 14 translocation. So I think what is going to happen in the future is that Venetoclax is going to get used in the context of a biomarkers test. So you'll test for something like the Bcl-2 and then you use the drug only in patients with high Bcl-2.

Cindy: Okay, and how about Selinexor, what do you think its use will be?

Dr Shaji Kumar: So again, it's a novel drug class. So, it seems to be active in patients where all other drugs have stopped working. So I think it's an important addition to the armamentarium or the arsenal that we have right now. The challenge, I think is the drug is associated with some major side effects like nausea and other GI problems. So I think it's a matter of time before people get more familiar with how to manage those side effects, and how to prevent some of the side effects from even happening in the first place.

Cindy: Okay, my last question, you've been so patient with me is, do you think dara plus a triplet will become the new standard of care for induction? Or do you think quads are going to be saved for later on during relapse?

Dr Shaji Kumar: So I think before the combinations we saw some very exciting data with the ALCYONE trial, there was an improved overall survival when daratumumab was added to bortezomib, melphalan and

prednisone. We already saw some data in the transplant setting that we could add daratumumab to bortezomib thalidomide, dexamethasone or lenalidomide dexamethasone and both are phase three trial, more deeper responses. But I think we really need to wait and see the longer term outcome to see if it's really worth adding that fourth drug in someone who's already going to transplant or is it more likely to be beneficial in somebody who's not getting a transplant. And more importantly, I think some of the trials are going to look at to see maybe that fourth drug is not needed for everyone. It's only needed in the setting where people are not responding nicely to the three drugs.

Dr Shaji Kumar: But it doesn't have to be daratumumab added to a three drug it could be any of those drugs added to the other two. So we know from the MAIA trial that daratumumab-lenalidomide-dexamethasone is quite effective for patients who are not going to transplant. So we could ask the same question, do we need to add bortezomib to daratumumab-len-dex or do we need to add carfilzomib to daratumumab-lex-dex? So I think the question of four versus three drugs, I think we still need to wait for a little bit more mature data before we start treating everybody with four drugs.

Cindy: Okay, great. Thank you so much for answering.

Gary: At this point, we'd like to open it up to questions from the audience. Shweta are you there?

Shweta: Thank you so much. I'll just move on to the audience questions now. We have quite a few questions from the audience list. But before that, I would like to announce out to the folks who are listening to the show online. If they would like to ask a question, they can dial in the show using 718-664-6574 and press one on their keypad. Or you can email your questions to shweta@trialx.com or post them on the page where you're listening to the show right now. I'll move on to the audience questions Dr. Kumar, we have quite a few questions. The first one says, I've been reading articles recently about adaptive therapy, which as I understand is more theoretical than clinical phase of work. I find it very interesting, and I would like to hear the panelists talk about their views on it.

Dr Shaji Kumar: So adaptive therapy, I just want to make sure that it's clear that we are talking about the adaptive therapy typically refers to where we can change treatment based on how a person is responding to the treatment. So for example, changing treatment based on whether somebody's going to get to be MRD negative, or looking at how the underlying clones have changed and then changing therapy accordingly. But we also have adoptive T-cell therapy, which is basically what we talked about just now with the BiTEs and the CAR-T cells and that is different. So the adoptive T-cell therapy, I think that is already what we are doing in the clinical trial, right now with those things. But there are several adaptive designs that we use for clinical trials where we are actually changing treatments. And I think that's going to be important because previously we didn't have lots of drugs so we kind of made with me, we had to make do with what he had. So there was limited flexibility.

Dr Shaji Kumar: Now that we have more drugs, different mechanisms of action, we can actually try and tailor the treatment better for the individual patients for more personalized therapy. I think that's where some of these clinical trial defense really come in.

Shweta: Sure. Thank you. Thank you, Dr. Kumar for the answer. The next question and I guess a couple of questions talk about absolute neutrophil count. So the question says I'm currently under treatment of Darzalex since September 2016 and Pomalyst since 2019 August, and last neutrophil counts were 1.38. How low can my ANC go before I need to worry about it? How can the ANC numbers be boosted?

Dr Shaji Kumar: Right. So the neutrophil counts, we get really worried when typically we try to keep it above 1000. And we get more worried when it gets to be under 500. Then the risk of infections really goes up. How can we deal with it or prevent it – One of them is to adjust the doses of medication. So for example, if somebody is on four milligrams of pomalidomide, and the ANC is dropping, we can do two milligrams and they might probably do equally well, but without a drop in blood counts. Especially when they combine different drugs and more likelihood that you're going to see this drop in the neutrophil counts. We can also

use growth factors, like the granulocytes called gCSF colony stimulating factor to try and boost the ANC numbers if they were to go down. But the preferred approach is to try and decrease the doses to see if we can prevent that from happening on treatment.

Shweta: The next question is also on ANC. The person is asking what do you know of intravenous vitamin C increasing neutrophils. When you're treating with chemo some of the breast cancer patients say that they did this for a few days after their chemo and each week the neutrophils raised for the lab results. So the person says I have neutrophils and I had to stop treatment twice as a result. And the lowest record was 0.69. So what do you think about intravenous vitamin C?

Dr Shaji Kumar: So there's clearly no data with vitamin C in the setting of myeloma, but what we also know is that vitamin C can decrease the effectiveness of some of the myeloma drugs, especially drugs like bortezomib. So I would be very cautious about doing something like that because it might decrease the effectiveness of the myeloma therapies. It's better to try and do the other approaches rather than go this route.

Shweta: Okay. Alright, so the next question asks, what do you think about the side effects that I have a very red face the day after RVD treatment?

Dr Shaji Kumar: Yeah, that is fairly common. I think a lot of the time it is because of the dexamethasone and that makes people quite flushed. And that is fairly common. So, that is probably what is driving it. Sometimes people can also get a rash from Velcade or lenalidomide but this sounds more like a dexamethasone related phenomenon.

Shweta: And the next question and I guess the last question is that I have read that there is a poor prognosis regarding 4; 14 translocation and IgG Kappa lambda inverse ratio. I was diagnosed in January, started treatment in October and on cycle 6. And the person says and I'm on a regimen of RVD and have had to stop twice because of low neutrophils. And what is your opinion regarding stem cell transplants now, or harvesting stem cells and doing transplantation later?

Dr Shaji Kumar: Right. So I think if you look at all the phase three trials, even with the RVD treatment, getting the transplant seems to keep the myeloma under control for longer than not getting transplant for the first set of treatment. So the preference right now based on the results from the phase three trial is to go for a stem cell transplant if the person is eligible for it. However, these trials also have not shown an improved overall survival for early transplant. So if they want to collect the stem cells and use the transplant at the time of the first relapse, and that is perfectly acceptable as well.

Dr Shaji Kumar: All right, sure. Thank you so much for all those answers Dr. Kumar. I think we have people online, who want to dial in and ask questions. Person dialing in from 3997 please ask your questions.

Caller 1: Thank you. I've noticed a lot of press recently, and I've been following CAR-T for some time, but the Chinese seem to be moving faster, much, much faster than the United States. Obviously, there's a little different structure there in terms of probably an oversight, but I've even seen articles of you can go to China and get a $70,000 CAR-T treatment. What's your take on that? And is there any collaboration with the results in what I would call much faster movement in China? I mean, from a patient perspective, we're all, there was the word Cure used in the title of this talk. I still haven't heard anybody say that on the talk, but I did dial in a minute or two late. I'd like to get a little bit of a perspective on whether I should be saving up my $70,000.

Dr Shaji Kumar: Right. So they have been quite active in terms of developing the CAR-T products and doing the clinical trials. Now, as you already alluded to this obviously less rigorous infrastructure for conducting clinical trials than what we have in the US. So there's always a concern from an individual patient safety standpoint. So I don't know if that is the advisable thing to do. Obviously, it's something that you need to talk to them, get more details about and find out what kind of results they have had so far.

Clearly, some of the results have already been presented, and some of them have been quite impressive. And the good thing is some of those things are starting to move into clinical trials in the US as well. So, for example, one of the first presentations or results from China was on the Legend Pharmaceuticals. And that particular CAR-T cell was taken over or bought by Janssen, who is now conducting clinical trials in the US.

Dr Shaji Kumar: So, irrespective of where it starts, I think the knowledge spreads fast. And those clinical trials certainly opens up in the US and gives access to people. So I think it is , I don't know if I can give you an adbasis to whether it's better to wait for a trial here versus try something in China. I think the devil in the details. Going back to the question of cure, are we curing patients with myeloma, we probably are curing a small fraction. And we have always been doing that and probably the proportion is gone up over the years. The problem is, there are no good tests that we can do to say that this person is cured of myeloma. And the only way to be sure that somebody is cured is now 20 years later, if it never came back without any treatment. Then we can say the person is cured. What we really need is a way to identify who is cured now rather than waiting for 15 or 20 years, once we are able to do that then we can start modifying our treatments to see how we can get people to that point.

Shweta: So probably we had quite a discussion in the last one hour and we have reached the end of our scheduled time today. So thank you so much, Dr. Kumar, for your answers. Audience, we were listening to Dr. Shaji Kumar of Mayo Clinic and patient advocate Gary Petersen, Jack Aiello and Cynthia Chmielewski, shared the latest research and disease specific treatment updates on multiple myeloma which were presented and discussed at the 62nd American Society of Hematology annual meeting, which is the world's most comprehensive hematology event held every year. We hope to see some of these new developments become fruitful in the form of new treatments that are not only available, but also accessible to ease the lives of multiple myeloma patients in the years to come. So Dr. Kumar, thank you so very much for your time and all the information that you shared with us today. Gary, Jack, and Cindy and the audience, thank you so much for your insightful questions that brought out a very informative discussion in the last hour. The talk will be available on curetalks.com. Please visit our website for details on upcoming talks. So until next time, thank you everyone and have a great day. Bye.