



Multiple Myeloma: An Insight into Early Intervention and Personalized Therapies

Myeloma patients are definitely living longer. A decade ago the median survival was 3 to 4 years, while now it is in the range of 8 to 10 years. With all the new drugs and treatments that have been approved, it is possible to control the disease for a longer period of time. We are talking to Dr. Shaji Kumar to explore the treatment potential of intervening early in the disease and also touch upon how personalized therapies can help in managing myeloma efficiently.

Full Transcript:

Priya Menon: Good evening and a warm welcome to everyone here. As Gary was saying myeloma patients definitely living longer and a decade ago the median survival was three to four years. Well now it is in the range of eight to ten years. So with all the new drugs and treatments that have been improved it is possible to control the disease for a longer period of time. We are talking to Dr Shaji Kumar from MayoClinic to explore the treatment potential of intervening early in the disease and also touch upon how personalized therapies can help in managing myeloma efficiently. We have myeloma survivor and editor of myelomasurvival.com Gary Peterson on the panel along with Jack Aiello and Cynthia Chmielewski, I extend a warm welcome to everyone again and I would like to tell the audience that we will be taking questions at the end of the discussion and you can dial in using 7186646574. Let us know if you have a question and ask them live or you can just post your question on curetalks.com or e-mail them to priya@trialx.com. Gary over to you.

Gary Petersen: Thank you Priya. Like I mentioned before it seems like it's a very timely to have Dr Kumar on especially with these two very important subjects which is whether to treat the myeloma early once it's found in the precursor states. And then also the whole concept of individualized medicine and what that means. For one thing I'd like to say Dr. Shaji Kumar is one of what I believe is a dream team that MayoClinic has put together and it's amazing what they've done. He's a board certified in internal medicine and his medical interests are obviously multiple myeloma and also Amyloidosis as well. He completed his medical studies and his internship at All India Institute of Medical Sciences in New Delhi and he's also completed two residencies in internal medicine. He's been involved with the MMRF and as well as the IMF and just about every other organization and you'll see that he is by far one of the premier medical professionals in the area of myeloma. So thank you so much Doctor for being here today with us. And another thing that I think is so important and it happened not too long ago, actually it was last year is that Dr. Kumar along with Dr. Nupur Raje and Dr. Jagannath had been in India and had put together a template or a consensus analysis of how to treat myeloma in India and with a billion people or so in India, obviously there's a need to come up with a standardized approach for India. So I think that was a wonderful thing that you did and then congratulations. At each of the myeloma meetings there was a debate as to whether to treat early or not to treat early and it's been I think in 2016 I was there and it was Dr Palumbo was debating with the French doctor and it seems like it comes up and it just most recently came up with one that's going on currently in Europe but I'm wondering with the successes of the Spanish group it showed the problem at Dex versus watch and wait was twice the life expectancy and also Mayo and Dana Farber successes doing the same type of thing with other drugs. Hasn't this been resolved? And if so why have we not seen some form of FDA approval for early treatment?

Dr Shaji Kumar: First of all Gary, thank you so much for the kind introduction. It is wonderful to be here this



evening. I think you bring up a very important point and I think this is probably the most debated topic in myeloma right now and can I just give a little bit of historical perspective? Now we know that all patients with myeloma start off with a monoclonal gammopathy of undetermined significance in markers. In some patients we can actually discern the phase that we refer to as smoldering multiple myeloma. Now for the longest time and for the right reasons, the typical approach for treating myeloma had been to treat only if it is starting to do some harm to the patient, any of those what we typically refer to as CRAB symptoms. And the rationale behind that was that the treatments we had were not curative and the treatments all came with significant side effects and some of the medications like Melphalan would even increase the risk of cancers in the long run. And then on the same only about 20% of the patients with markers and maybe about 50 to 60 % of the patients with smoldering myeloma would have disease progression in the long run. So there's always the concern to be treating some patients who might actually live their normal life without ever needing treatment for myeloma. So for all the right reasons it was a conservative approach for the longest time. Now what has changed in the past few years are several things. One, we understand the disease much better, we understand better how the transition happens from the markers to smoldering to myeloma. We have better tools to try and predict which patients are at the highest risk of progressing to myeloma. So the first step in terms of changing our approach was the change in the diagnostic criteria that happened three years ago where we said yes. These patients have, if you have certain features then your likelihood of moving from smoldering to active myeloma is over 80% in a short time span of two years.

So we always felt that is probably a threshold that we all feel comfortable with that we don't want to wait for the other shoe to drop so to speak. So we felt that the possibility of harming patients is very low if you use that criteria for starting treatment. So we move that line a little bit so that now we start treating patients before actual symptoms start but more because we can accurately predict who is going to get the symptoms. Now that only takes care of or only covers maybe some were between 5 and 10 percent of patients with smoldering myeloma. So the other 85 to 90 % of the patients with smoldering myeloma we at this point still don't want to treat because again the question is are we going to harm these patients? So then the Spanish group did the trial that Gary just referred to. It is called the QuiRedex trial where they took patients with high risk smoldering myeloma and this is using criteria that have been shown in the past to identify maybe a 50 % risk of progression over the next five years. So what they did was to treat half of the patients with Revlimid, Dexamethasone and the other half of the patients were just watched as we used to do before. And they showed that the patients who got the Revlimid and the Dexamethasone had a better survival compared to the people who were just watched. Now you may ask if you have the data why aren't we doing that in our day to day practice? And I think that is exactly the question that Gary was referring to. Now the problem with that study there are two problems. The biggest problem is for almost a quarter of those patients probably had active myeloma by the current definition. So they should really have been treated and not necessarily watched. Obviously we didn't know at that time. But from the subsequent study they did they realized that anywhere from 25 to 30% of patients whom we call smoldering myeloma actually have active myeloma, if only we did imaging steady scan to look at the bone something more sensitive than the skeletal surface. So that's one problem with that study. The second problem with the study is it's a relatively small study for us to be changing our entire practice that would affect thousands of patients. So we do need at least one more confirmation of that finding, in a separate study and that study has already been completed that is the ECOG trial that compared Revlimid vs no treatment and hopefully we'll hear something back from that in the next year or so.

However even though we won't apply the results of the QuiRedex trial into practice it still gives us very important information. One of the biggest concerns we always had is we actually might make the myeloma more resistant to the normal treatment by treating them early. And the QuiRedex trial showed that people who actually eventually ended up getting treatment for myeloma the initial treatment did not seem to have had any impact. And they still continued to do better. So at least the QuiRedex trial started feeling the first layer of by saying yes you are not harming anybody. Now we need another trial to be the next layer of proof



that we are actually benefiting people or confirming that finding. And if I were to do it make a bet I would bet that it's probably that is probably going to be the approach of the future. We just need to identify where do we draw the line so that we actually benefit more people than we harm.

Gary: So you say that you mention that there's a couple of questions that need to be answered and one of which is who to treat, and you pretty much talked about that. Now there's also another one is how to treat it is it REVLIMID – Dexa there's other trials in process that look at the curative approach?

Dr Shaji Kumar: Absolutely. I think that's a very very important point. So I think after starting to explore whether we should be treating patients with high risk smoldering myeloma, there's also a similar debate going on as to what is the right approach for these patients. So you could think about it two different ways. And we don't know which would be the right approach but one approach could be that you take the patients with the high risk smoldering myeloma give them a very light treatment over a long period of time, to try and prevent the smoldering myeloma from becoming active myeloma. So that approach is kind of a more conservative way of looking at it, that we actually minimize any any kind of side effects. Not the opposite but a different perspective on the same thing is if this cancer is indeed in the early stages and more amenable to treatment why don't we give the best treatment that we have for myeloma but for a limited period of time and potentially get rid of most or if not all these cancerous cells that we essentially are looking at curing the disease or nipping it in the bud which is what we do for a lot of other cancers like early stage breast cancer or early stage prostate cancer sometimes. So I think those are the two different perspectives that are being looked at in the clinical trials. So there is the Revlimid type trials that we talked about, there is Daratumumab type trials that are ongoing. Then there's also the more curative type approach. So there's the Spanish trial that we already know some of the results of which looked at using again combination of Carfilzomib, Lenalidomide, Dexamethasone and stem cell transplant to see if we can cure the disease and we're doing a trial called the ASCENT trial which is basically not going to use transplant but trying to see if we can achieve the same thing by replacing the transplant with a monoclonal antibodies like Daratumumab. So instead of using transplant we are using Carfilzomib, Len, Dex but add Daratumumab after that. So the ongoing trials I think will give us a good sense as to which might be a better approach but we still need the large Phase 3 trials.

Gary: Ok, thank you. In the end however if we can if you can't find it you can't treat it and late diagnosis is one of the biggest problems with myeloma and I know they're trying to look at that based on an IMF I stop multiple myeloma in Iceland and how do we find it, how do we get it to where it's not in the stage 3, that it's not that you're not near death by the time you find out exactly what it is?

Dr Shaji Kumar: No I think the whole concept of screening for a disease to catch it early on obviously is something we always try for in all cancers and myeloma is probably the best example because we know it takes anywhere from 10 15 20 years for it to go from the markers phase to the myeloma phase. So the Iceland project is really trying to see if you can just screen the entire population and see one how frequently does it happen, what stage do we find them in and what are the risk factors for developing this and where the disease to progress and so forth. So the biggest issue with screening as a concept is that when you screen and find something you should be able to do something about it. So the crucial thing that myeloma right now is if we find it what do we do with it. So we know that 80 % of the people in whom we find that monoclonal protein nothing will ever come off it but then they could have significant issues in terms of just carrying the burden of knowing that you have something that could become the cancer. And also all the other things that go with it in terms of healthcare coverage and so forth. So that's something we need to think about when you think about screening everyone. The second is if we've had a really really good tool to put people into OK you have the protein but your risk of getting myeloma is less than 2 % in your lifetime and somebody else you can say yes you have a 90 % chance of getting myeloma in the next three years. Then we know we're going to do things differently for those people. So I think the first step towards making screening is going to be a universal thing is to 1, identify at what age do you want to do it. Second, if you find something, we have a much clear approach as to what we do with the result and all these trials especially



the ones with smoldering myeloma, they consistently show a survival improvement, an overall survival improvement and that you're making people live longer then you greatly strengthen the need or the justification for screening programs.

Gary: Well said, now another thing that we were to discuss today is personalized medicine and we hear a lot about it but in the case of myeloma we really haven't, historically all the patients have been given over the course of their disease, all the drugs that are currently available and also anything in clinical trials that might be helpful. So when and how will this change or is it changing now?

Dr Shaji Kumar: Yeah so big question. So I mean the goal eventually is we want to try and match the drug to the patient or even if we know that all the drugs in myeloma doesn't work for every patient and we don't have a very good way to identify ahead of time if a particular drug is going to be beneficial for a patient. Now up until now we had just had a handful of drugs especially if you think about the classes of drugs, we had the proteasome inhibitors, we had the immunomodulatory drugs, we had the monoclonal antibodies and then you had the traditional chemotherapy drugs, and the HDAC inhibitors and so forth. And so when you have a limited number of drugs available and you have a disease that keeps, that has the relapsing and remitting course we eventually end up using everything in different order. So two things can change. One is even in the current scenario if we can identify which treatment is going to be the most beneficial we could potentially give that in the beginning and get the maximum benefit out of it before we go down the lane to do the next treatment. But I think to make it truly personalized medicine in the future we need two pieces. One is more drug with very very clear mechanism of action and two a drug that identifies the patient that's going to respond to that drug. I think we're going to starting to see that, a best example is probably the Venetoclax. Now this is a drug that is approved for treatment of chronic lymphocytic leukemia and it acts by binding to a protein that allows these cells to survive or the cancer cells to survive. And we know that patients at the translocation level 14, about half of them will respond to this particular drug. And there are some biomarkers that are being developed. So this is probably going to be the first example where we would do the test, find out that patient has that particular profile that is likely to lead to a response. And then we treat the patient with that with that drug. Now there are other approaches that are looking at the mutation that happen in myeloma. We know that there are about 10 or 12 mutations that are often found in myeloma cells, even in a given patient it may not be present in all myeloma cells but at least some of them. Now there are clinical trials that are looking at trying to see if we can get a drug that specifically attacks the cancer cell that carries that mutation and given the fact that myeloma cells can have multiple different mutations and also that these things can evolve over time, the future might be that even find the top two clones or the top three clones and then try and use a combination of two or three drugs that targets those clones. So I think that would be the next step. But right now there's a trial called My Drug that is being started by the Multiple Myeloma Research Consortium that is going to look at patients with high risk myeloma and try to use these targeted drugs in combination with the standard treatments to try and see if you can make make a dent.

Gary: Very good. Well thank you. There's so many things seems to be happening so quickly all the new drugs that have been developed. All the great things that appear to be coming down the line like CAR – T and MILs and many other things like that which are very specific to the disease so we're all obviously quite hopeful. What I'd like to do now is to open it up to the folks online, the other members of the program, Jack are you online?

Jack Aiello: Yup, I'm here and I'm ready to ask questions. Dr. Kumar it's always nice talking with you and I really appreciate your being on this call. When you look at these trials for smoldering patients typically they are for high risk smoldering patients and after reclassifying ultra high risk smoldering patients as multiple myeloma, can you clarify what that definition is of high risk smoldering myeloma and has that definition been standardized yet?

Dr Shaji Kumar: Yes. So there were two questions, one is do we know who are the high risk among the remaining patients. And remember that the new definition probably only moved somewhere between 5 and 7% of patients from that smoldering myeloma group into the active myeloma group. So we still have the 90-95% of the patients still called smoldering myeloma. Now the same factors that we used to use for high



risk smoldering before, like the quantity of the M Spike, the Free light chain ratio ratio, the monoclonal plasma cells from the flow cytometry and so forth those things still hold true. We recently took a look at the Mayo data and this is actually going to be coming out in the near future. But we found that the same factors still held true but then the numbers have changed a little bit. So instead of a ratio of eight, now maybe a ratio of 20 might be more appropriate. So this is kind of a first stab at trying to see if we can modify the high risk criteria taking into account those truly high risk patients who are moved out of the group. But I think the definitive answer is going to come out of these International Myeloma working groups smoldering myeloma study that we are doing. So we have already collected data from about 2000 smoldering patients across the world and we're still continuing, our goal is to see if we can get anywhere up to maybe 3500 or 4000 patients with smoldering, whose data that we can collect and then we can look in that dataset and say this is the definitive way of identifying the high risk smoldering melanoma patients. So we're hoping that we can say this is maybe from this effort it might be the 5 or 10 % of patients we might end up reclassifying as myeloma but we're hoping that we could save this group of patients have a 80 % risk within the next 5 years. These patients have 50 % of them the next 5 years. And these patients have 20 % risk in the next five years. So the intensity of the treatment in the clinical trials could also be different depending upon whether if you use this kind of system to design your trials.

Jack: Thank you. My next question I think you've already touched on it but I remember years ago that Vincent Rajkumar put out a paper about control versus cure for myeloma and I guess that same debate is going on for smoldering myeloma and you talked about aggressive versus non-aggressive therapies and such. Can you tell me where do you kind of fall into that time or that line for treating smoldering myeloma?

Dr Shaji Kumar: So I firmly believe that the future it will bear out that treating smoldering myeloma or at least a group of patients with high risk smoldering myeloma, early is the way to go. But I think I would hesitate to do that right now outside of a clinical trial because of all the reasons that I outlined before. I think at the end of the day we don't have tools which are, we have tools that are reasonably sensitive but we don't have tools that are very specific. It's hard for me to tell a patient that you have a 95 % risk of getting myeloma in the next year for the vast majority because we just don't have that specificity right now. So I think it's a question of getting the right tools. So I think what you just referred to, just getting that standardized approach for defining high-risk is going to be a huge next step before we start feeling comfortable treating a group of these patients.

Jack: And then with immunotherapy being today's hot button if you will. Would you ever consider treating a younger smoldering patient with an allo stem cell transplant so that the patient receives a new immune system and likely handled GVHD better?

Dr Shaji Kumar: Not at this point. I mean I worry that when you think about patients with myeloma who go through an allogeneic stem cell transplant, the five year survival is 35 %. Now I think first I need to have a verification that the current standard treatments actually do make a dent in the risk of progression for these patients before I would move to something that is so much much more aggressive and likely to have its own side effects so the short answer is no I would not consider an allogeneic transplant for a high risk smoldering today. But that is a very very valuable question that I think we should ask at some point once we feel comfortable the concept of treating.

Jack: And then my last question falls up on Gary's question about personalized medicine and you mentioned that we really do need more drugs to that are effective against certain mutations. But the way myeloma seems if you have a given mutation it doesn't appear to me that a single drug will help, it'll still be drug combinations don't you think?

Dr Shaji Kumar: Oh I think so, knowing how much these clones escape, I don't think we will ever be able to get away with just one drug for myeloma. But what we're hoping is that if you know that this is the major clone of the disease, maybe adding this will help us get rid of the top two clones for example, by combining it with the standard treatment.



Jack: Got it. Thanks so much for the answers and I'll turn it over to Cynthia.

Cynthia Chmielewski: Yes I do have questions. First of all thank you Dr. Kumar for spending some time this evening, it was great listening to you and your insight. I guess I just want I can talk a little bit that I guess a few years ago the Fund research initiative started with the two pathway trials to smoldering myeloma, the ASCENT trial and the FUTURE trial. Can you just give us a summary of what those trials were and are they open and enrolling, what's happening?

Dr Shaji Kumar: Yep so the trial is the one I can't speak too much I'm not very clear about that the same for the other one. But the ASCENT trial is then essentially, we've been wanting to open this for a while it's taken quite a bit of time because again it's gone back and forth with FDA originally we wanted to try and do some transplant as part of it. But we got strong pushback from the FDA that maybe that's not the right thing to do right now which is fine. So what we ended up deciding to do is take patients with high risk smoldering myeloma and treat these patients with a combination of Carfilzomib Camfetamine-Lenalidomide-Dexamethasone and Daratumumab drive to them. So we believe the combination of these four drugs represents one of the most effective agents that we have right now. So we will have high risk smoldering patients receive this treatment for an initial one year with more intensity and the next one lower intensity more of a maintenance phase but give treatment only for two years and then stop and we will look at what is the risk of getting myeloma what is the probability of getting a minimal residual disease negative status and then also you just want to look at the natural history of what happens with patients with smoldering myeloma. So the hope is that you can actually demonstrate that this can be cure some of these patients if that does happen then we would like to take it forward into Phase 3 trial.

Cynthia: Ok, so now is this trial open yet or is it...?

Dr Shaji Kumar: So it is right now going through the initial what you call the site initiation visit. So we have about 10 centres that it's going to open up. We have already had the initial pretrial opening meetings with both the Indianapolis and also at Moffett.

Cynthia: Ok. and is it a single-arm trial or a randomized trial?

Dr Shaji Kumar: It's a single arm trial.

Cynthia: Okay so everyone will get the treatment for a couple year period. Okay great. So we'll have to keep updated on that one. My next question is ASCO is coming up in a couple weeks. Are you expecting any exciting or practice changing news about myeloma.

Dr Shaji Kumar: Well I don't know if any of it will be practice changing but certainly there will be some



interesting data coming out, I guess we will have to wait and see the whole detail before really understanding what it means to practice.

Cynthia: Ok, my next question is if I knew someone who was newly diagnosed with smoldering myeloma what would you tell them as to what type of diagnostic testing they should be getting, what type of genetic testing they should be getting, what kind of surveillance they should be getting, because many times when someone who's diagnosed with smoldering myeloma are diagnosed willfully by a local doctor, it seems to be oh don't need to worry about anything. I'm thinking that that's not the case. So what would you tell someone newly diagnosed with smoldering myeloma?

Dr Shaji Kumar: Good question. So I think the first thing is to make sure that we are dealing with smoldering myeloma and not myeloma that needs treatment. So I think it's important that in addition to the usual blood test looking at the M Spike and so forth and the urine tests, they also need what you call at least the advanced imaging studies. So either a PET-CT or an MRI of the spine to make sure there are no other lesions that suggest that this may be more of an active myeloma and not a smoldering myeloma. And in terms of the genetic testing obviously the bone marrow biopsy right now I think we should at least get the FISH testing done on all these patients. The importance of the mutations for example on the risk of transmission of smoldering, it's still pretty unclear. So we'll have to wait and see the data before we do anything with it.

Cynthia: And then how often should they be like their blood should be tested, how often should imaging be done like, what would be the surveillance schedule for someone with smoldering multiple myeloma?

Dr Shaji Kumar: So I think that for smoldering myeloma, the first time you see the protein you definitely want to do it at least three months later. And after 3 months, if it doesn't show any change, initially at least every two to three months you want to check it to get a sense of the trend. If it's pretty flat then you could probably ease out a little bit to maybe every three to four or three to five months, repeating the protein.

Cynthia: And it should just be that blood tests or are there any other testing that should be done like imaging later on or vital marrow biopsies anything like that, or do you think what is just enough for smoldering myeloma population?

Dr Shaji Kumar: Yeah I think on a routine basis like every 3 months doing a blood test is sufficient. But at least once a year or once every 18 months it's reasonable to think about doing either a low dose whole body CT scan which doesn't expose patients to a lot of radiation but still is very sensitive to picking up abnormalities in the bone. So I think that periodically doing that would help.

Cynthia: Okay that sounds great. Also I was wondering is there, I know you've been talking about this, but is there any progress being made through any of the trials or studies, the observational studies happening that's allowing us to become better at predicting when MGUS for smoldering myeloma will move to active myeloma. And for people who are interested in contributing to that research is there places where people can enroll in some type of registry who have smoldering myeloma that could help make that projection in the



future?

Dr Shaji Kumar: Yeah I mean there's a whole lot of different registry type studies that are ongoing. We have, looks like most of the large institutions, academic institutions have these sort of studies ongoing and there's also a lot of interest in trying to have some of these registered even started by the National Cancer Institute. So yeah I think it's best to try and find out which ones would be the closest to the individual.

Gary: Thank you Cynthia. Priya could you bring on the folks who are online or talk about the questions that have been submitted.

Priya: Thank you Gary. We have some callers who've lined up to ask Dr Kumar some questions. Person calling using 7414487, please ask your question. Person calling in 3102127 please ask your question.

Caller 1: Yes I was just I am a smolderer and I'm interested in starting a trial. I'm not a high risk. And I just wondered what Dr. Kumar's thoughts were on, there's maybe one or two trials out there now for smolderers who aren't high risk, what he thinks about that?

Dr Shaji Kumar: So most of the interventional treatment types for smoldering have been directed towards people with some kind of high risk smoldering, whatever definition is used. As I said in the beginning until we have some information saying that the high risk, the truly high risk myeloma is benefiting from treatment I would be a bit hesitant on recommending treatment definitely but in the clinical trials it's perfectly fine. I'm guessing that most of the known high risk smoldering myeloma trials are looking at interventions which are very low risk of side effects. So I think it's certainly reasonable if you have a trial that you can access. I would strongly encourage participating in the trial

Priya: Thank you Dr. Person calling in using 7414487 please ask your question. You are on air.

Caller 2: I read one time that a patient said the doctor proposed the induction therapy to be say, Revlimid, something else and Dexamethasone. Well out of two of those but I don't want to take Dexamethasone and we can see how this goes. And then maybe down the road if we needed I'll reconsider it. But the patient didn't like the side effects from the Dex. So I realize the patient could be his own or her own advocate for the reactions but it depends on a lot of factors like the type of myeloma or the aggressiveness of it but one is that something reasonable and secondly it seems that steroids including dexamethasone can cause osteoporosis and since myeloma destroys bones anyway and that it seems like it's doubling the impact to the plus the phosphonates are given to keep the bones together. So it seems like you're hitting the bones in two different ways. One you're tearing them apart by using Dex and patients may or not even be informed of that. But on the other side of the coin you're trying to preserve the bones with the phosphonates. Could you talk about all those factors and what your opinion of using the Dex sir?



Dr Shaji Kumar: So you're thinking about in the context of smoldering myeloma or generally in myeloma treatment?

Caller 2: I'm sorry I know this is beyond the smoldering stage. Like I don't know. I actually myeloma has been confirmed in the patient and is beyond the window for smoldering. Thank you and I appreciate your answering and the time on your presentation.

Dr Shaji Kumar: Okay. Yeah. . You're welcome. So that's an important question that we have to start asking how much do we really need the Dexamethasone. Unfortunately all the data that we have up until now has been in combination the Dexamethasone and we know that all the myeloma treatments work much better with the dexamethasone than without it. We did in fact do a clinical trial where we treated newly diagnosed patients with Revlimid alone, without Dexamethasone and then added Dexamethasone only if there was no good response. I can tell you the overall result of that approach was not as good as what we would have gotten with Revlimid and Dex started together. So that's one. But obviously the caveat there is we are just combining Revlimid and Dexamethasone. What about if we did Bortezomib Lenalidomide and then remove the dexamethasone from that combination? We don't know the answer but certainly right now we are doing trial a where we are combining Ixazomib Lenalidomide and Dexamethasone along with Daratumumab. But the Dexamethasone is only given for the first two cycles and then we stop it. So we are trying to see if we have really effective drugs like Daratumumab, a proteasome inhibitor like Ixazomib and an immunomodulatory drug like Lenalidomide. So three of the major classes of drugs in one package then maybe we can do away with Dexamethasone. So I think that those are the kind of trials which will hopefully going forward tell us what is the best way to deal with myeloma without the Dexamethasone.

Caller 2: Could I ask a follow up question? I know the induction periods vary from patient to patient but let's just say the average one is six months. Is that a period of time where the Dex could cause osteoporosis?

Dr Shaji Kumar: No. I mean any amount of Dexamethasone over time will cause some slightly weakened bones but six months of the induction therapy with the dexamethasone especially when you are getting the bisphosphonates and everything. I'm not too worried about the impact on the bone. I just want to make sure that patients get the best treatment possible.

Caller 2: Sure. And is it typical for myeloma patient who gets that kind of induction therapy with Dexamethasone and because of the the the hard impact, is it typical to be for the oncology doctor to work perhaps with an endocrinologist or other bone density or mineral density skeletal type of doctors or specialists to monitor the bones because it seems like if it's not you need a DEXA scans to see the density of the bones and doesn't seem like that occurs very often with physicians who are like oncologists who are working to cure the myeloma part but maybe I'm wrong maybe that's changed. Can you comment on that at all?

Dr Shaji Kumar: Yeah, no I think you know myeloma unlike many of the other, particularly a multidisciplinary approach is what we need because you have kidney problems they often need nephrologists, the bone problems require the help of an endocrinologist and so forth. So I think it varies, in our own group we have



an endocrinologist who is part of myeloma group. So we are quite fortunate to have that arrangement. But I think it's important to be proactive about the bone health daily the using the bisphosphonates or the other similar drugs that strengthen the bones. It's clearly something that should be integral part of myeloma management irrespective of whether they have OPS bone disease or not.

Caller 2: OK Thank you very much. I know I have taken up a lot of time. Appreciate it, if I have a chance to ask further questions I will. Thank you very much Doctor.

Priya: Thank you. We had some questions on that side as well Dr. Kumar. Is there a MM genetic profile that is susceptible to cure by a particular triplet or quadruplet drug protocol?

Dr Shaji Kumar: So we don't have any genetic profiles that we know is going to be the most likely to benefit, on the corollary, we do have some genetic profile for the high risk patients where we know the current state and wont do very well. So I think that's what we need to focus on to try and see if he can translate that information to treatment decisions.

Priya: The next question is when will liquid biopsies be FDA approved for multiple myeloma, also, will it be a valuable tool for genome sequencing too?

Dr Shaji Kumar: So I think the liquid biopsy it still is a little away. I think they're just starting to scratch the surface of the what we can achieve with that. But I think it's very promising and I'm quite hopeful that in the future we will be doing a lot less bone marrow biopsies than we had in the past.

Priya: OK. And next question is from Manjunath who writes in, what really does heterogeneity mean is this heterogeneity in the same antibody type, whereas a different variable portion or epitopes of the same exact antibody class or is this heterogeneity due to monomers and dimers or pentamers or does this refer to oligoclonal or does the heterogeneity refer to biclonal or triconal? Can you explain clearly what the difference is with an example?

Dr Shaji Kumar: Well the heterogeneity is definitely used in multiple different from a different perspective. Typically when we talk about the myeloma being a very heterogeneous disease is because of the clinical behavior that two identical looking myelomas can behave very differently so it's obviously a collection of different diseases so to speak which are all bunched under the diagnosis of myeloma. But even within a patient it can be quite heterogeneous because you can have multiple clones that all behave differently and respond differently to different drugs. So I think it's got a multi-dimensional definition when you talk about heterogeneity.

Priya: That's the last of the questions. If you have a question for Dr. Kumar please press 1 on your keypad and we can bring you on air to ask your question. We do have some time more. If the panel has any questions, probably we can have another round, Gary you are on.



Gary: Jack do you have another question?

Jack: I'm okay. Mine has been answered. Thank you.

Gary: Okay. Cindy?

Cynthia: I'm fine for now, I'll start thinking now.

Gary: One of the drugs, there's a couple of drugs that are coming up which I just read something Dr. Kumar that this Selinexor seemed to be a drug that showed some positive results in penta refractory patients which it gives them another possibility. So do you what do you think about Selinexor?

Dr Shaji Kumar: No I think the results that we have seen so far is quite encouraging, certainly patients who have stopped responding to all the other drugs still seems to at least maybe 20 % of those patients that's going to Selinexor. So I think there's promise there. There's also issues with the side effects that we need to learn how to manage.

Gary: There's also another one which is kind of off the radar that I noticed but I know that the Seattle Cancer Care and Dr. Ahluwali Mayo and in Jacksonville is looking at and it's called CLR 131 and it happens to be apparently a drug that carries a little molecular package I guess and it goes after the... yeah. Could you explain that? Is that something that is ready for primetime or no?

Dr Shaji Kumar: Oh I don't, I mean it's a way of using a radioactive substance close to the myeloma cells to try and see if we can get rid of it. I think it's very early on, it's really too soon to say if it's going to have any benefit or not.

Gary: Well I noticed that in the early studies that it said that they had a 30% benefit rate and that the overall survival – progression free survival was like, or maybe it was overall survival was like 24 months and growing so that it was as good as what they saw with their tumour maps. So that's why I asked that question because early indications are that it's it's an amazing possibility.

Dr Shaji Kumar: Yeah and I guess you have to stay tuned.



Gary: Yeah exactly. OK. Do you have any other any other drug that is coming down the pipe?

Dr Shaji Kumar: The other one obviously that the BCMA antibody that was presented at ASH from GlaxoSmithKline is very interesting to see similar other antibodies from other people too. Then there are bite platforms again targeted towards BCMA, the bi-specific T cell engager drugs that theoretically should have some good activity. There's a new IMiD or immunomodulatory drug like Pomalidomide that's going through clinical trials seems to be of interest. So I think there's quite a few.

Gary: You got that new Melphalan?

Dr Shaji Kumar: The Melflufen? Yeah that is also I think early on I mean I'm sure it will work. I mean the question is we need to find out how differently does it what advantages does it have over the other agents.

Gary: So a lot of great stuff coming down the pipeline as well.. It's amazing what you guys are doing. So keep that dream team dreaming.

Priya: We have two more callers Dr Kumar, who want to ask question. Person calling in using 2199090 please ask your question.

Caller 3: Yes thank you I am Eric. You touched on this a little bit. Dr. Kumar But is there any rationale for example at first relapse. Is there any rationale really for going with one of the standard FDA approved triplets knowing that I think all the research now is that that's a holding action and that will only last for maybe a year maybe two. Is there any rationale for using those triplets rather than going for quadruplets and going for the home runs so to speak on the relapse patients?

Dr Shaji Kumar: We don't know if a quadruplet is going to be a home run either. So I think that's what we need to study in the clinical trials. What we have learned in the past is adding more drugs to a cocktail doesn't always translate to better results, for several reasons. One is as you add more drug, there's more side effects and then you actually end up decreasing the dose of maybe the more effective drug. Second is drug could work against each other in the combination. So there are all those things are unknown until you actually do clinical trials. So I think even the four drug quadruplet data that we have so far it's so early on it's really hard to know how much that for the drug is adding to it but I think we are going to struggling with the question. Let's say if you have a combination like VRD or KRd and now you have Daratumumab so do you just add that to it you or do you just add to it and take something else out of it which would be a better approach. We don't know.

Caller 3: Ah I see. Okay. And the second question is what testing do you do at first relapse and then during treatment, how often do you repeat which tests? Are you always looking for mutations to arise or can you



just?

Dr Shaji Kumar: So we do we certainly do a FISH test to make sure there's no new 17 B deletion or 1 amplification and things like that but also in some of these patients we do have the access to look at the mutation panels and we use that especially in patients who have stopped responding to some of the common drug.

Priya: Thank you Dr. The next caller is 91836086 please ask your question.

Caller 4: Hi this is Manju thank you very much. Dr Shaji Kumar. I have a follow up question on the answer that you provided earlier. So I have two questions. The first question is the heterogeneity that you said I wanted to find out if let's suppose somebody has IgG Kappa. So are you saying that the multiple clones are all clones within the IgG Kappa itself or could it be like IgG Kappa and IgG Lambda because I thought that would be considered as biclonal. So this one you are saying that heterogeneity is within IgG Kappa itself.

Dr Shaji Kumar: Correct. So within each of those there will be heterogeneity.

Caller 4: Okay okay. So then the second question that I had was in a certain patient close relative of mine before the start of chemo the analysis the free light chain assay showed a thin discrete band in IFE corresponding to the beta region. It was showing elevated Lambda free chains. Post chemo after three and a half courses what is being observed is the IgG Lambda before chemo it was just elevated free lambda chains, now everything is normal but IFE is actually showing IgG Lambda in the gamma region. So would you consider this as oligoclonal band or what do you think this is is this biclonal?

Dr Shaji Kumar: Yeah that's a good question. I mean it's hard to know for sure because it's also a lambda, so it's quite possible that you had the very faint IgG Lambda to start with and this was kind of buried by the bigger side of the light chain. So the discrete band that was seen in the beta region is the lambda light chain. So it could be either of the two. And when you have this kind of the same isotypes and it's sometimes much harder to be sure. So we'll just have to continue to watch that.

Caller 4: OK thank you very much. Really appreciate it Dr Kumar.

Priya: Thank you Dr. Kumar. Thank you very much for sharing all of the information with us. So we are almost at the end of time Gary Jack and Cindy, thanks for the great questions. And this talk will be available with the transcript for playback on curetalks.com. Thank you and have a great evening.