

History and Future Initiatives for High Risk Smoldering Myeloma Cure

For this second talk in our high risk smoldering myeloma series, we have Prof. Jesus San Miguel from University of Navarra, Spain discuss his team's investigations into high-risk smoldering myeloma and probable cure. For patients with smoldering multiple myeloma, the standard of care is observation until symptoms develop. However, this approach does not identify high-risk patients who may benefit from early intervention. Our myeloma panel is talking to Prof. Jesus San Miguel about his research, clinical trials in the pipeline and future of myeloma treatment.

Full Transcript:

Priya Menon – Good afternoon and welcome to CureTalks. I am Priya Menon, Scientific Media Editor of CureTalks, joining you from India; and today, we are talking about multiple myeloma. This is CureTalks' 111th episode. On the panel are myeloma survivors and advocates, Cynthia Chmielewski and Jack Aiello. The talk is being co-hosted by myeloma survivor and advocate and editor, myelomasurvival.com, Gary Petersen. This is our second talk in the series on high-risk smoldering myeloma. In our previous episode, we had Dr. Shaji Kumar from Mayo Clinic discuss the nuances of the upcoming ASCENT clinical trial. For this second talk today, we have Prof. Jesus San Miguel from University of Navarra, Spain. He will be discussing his team's investigations into high-risk smoldering myeloma and probable cure. For patients with smoldering multiple myeloma, the standard of care is observation until symptoms develop; however, this approach does not identify high-risk patients who may benefit from early interventions. Our myeloma panel is talking to Prof. Jesus San Miguel about his research, clinical trials in the pipeline, and future of myeloma treatment. Before I hand over to Gary, I would like to remind the listeners that we will be addressing questions sent in to us at the end of the show. If you have a live question for doctor, please press 1 on your keypads and let us know and we will bring you live on air to ask your question. With that, its over to Gary.

Gary Petersen – Yes, and I am so, so happy to be able to introduce Dr. San Miguel. He is the Head of the Hematology Unit at the Universidad de Navarra and the Scientific Director of CIMA, and the Vice-Dean of Research at the University of Navarra. I had a whole long introduction, I am going to give it the Cliff notes version and just say that Dr. San Miguel happens to be among an elite class of myeloma specialists throughout the world with people like Dr. Richardson and Dr. Barlogie, Dr. Palumbo and the like who are just at the very tip of the spear and are exceptional myeloma specialists and we just thank God that they are there, helping us get through those very, very difficult disease.

Gary Petersen – Now, Dr. San Miguel, in recent years like immunotherapy, other treatment has taken center stage? Can you give us the logic for early treatment and specifically in high-risk progression smoldering myeloma?

Prof. Jesus San Miguel – Okay. Thank you very much. It is my pleasure to be with you. As you mentioned, yes, its like a long story working on multiple myeloma. I did my PhD thesis in 1980; and since then, I have been working in this disease and I can say the first message is going to be a positive message because the outcome of myeloma patient has changed dramatically from the 90s until today and now there is a clear hope for myeloma patients with a good proportion of patients that probably can be cured or at least to convert this disease into a chronic disease. Returning to your question about high-risk multiple myeloma with high risk of progression, this story also started many years ago. We reported in 2007, that's almost 10 years ago, that we think that smoldering patients, there are different categories. There are low risk, there are intermediate risk, and there are high-risk smoldering patients and these high-risk smoldering patients can be identified with different methods. One is the major classification, that are those patients that have more than





30 g/l as well as more than 10% plasma cells, when they say 30 g/l of M component of paraprotein and more than 10% plasma cell in the bone marrow. There are other classifications – the Spanish classification, the PETHEMA classification, that identify these high-risk patients by using multiparametric flow cytometry when the majority of these plasma cells is..., whatever their proportion is, but when all these plasma cells are clonal, they are high risk to be transformed and when I talk about high risk, this means that these patients, half of these patients, 50%, will transform within the first two years. This is what we consider now high-risk smoldering patients.

Prof. Jesus San Miguel – If you ask me for the rationale for treatment in these patients, I think this is obvious. In the past, we did not treat every myeloma or high-risk smoldering patients mainly because most of the treatment was ineffective. By contrast and also because at that time, we were not able to discriminate between the low risk or intermediate risk that are likely to benefit from early intervention from the high-risk multiple myeloma or the ultra high-risk smoldering multiple myeloma patients that are the ones that may benefit from early intervention and in fact, in these patients, if you have 50% or 80% risk of progression of transformation into multiple myeloma within two years, probably most of the patients will not like just to wait until they develop symptoms. They will prefer to avoid the symptoms and to be treated early on. I always try to compare this situation with breast cancer or prostate cancer. As soon as you detect the disease, you would like to avoid, you want to avoid the transformation into an aggressive or metastatic breast cancer. So, it is similar, just have to visualize for the high-risk smoldering and for this reason, we decided to conduct clinical trials in this population, not in the rest of the smoldering patients. We are concentrating only in the high risk or ultra high-risk patients.

Gary Petersen – Great! Well, thank you, doctor. Dr. Ghobrial of Dana-Farber has also been working on this; and she once stated that early treatment must show an overall survival benefit in the clinical trial setting before any benefit for early treatment can be exhibited, meaning that if there was previously many trials, several trials that were unsuccessful to show any benefit in survival, including an IMiD, which was thalidomide, yet your lenalidomide-dexamethasone trial was the first to show this survival benefit and can you explain these results?

Prof. Jesus San Miguel – Okay. The explanation, I think, is quite simple and it is because in the previous trials, they don't..., they didn't identify the high risk as smoldering. They included all smoldering patients. By contrast in lenalidomide-dexamethasone, we focus only on the high risk because we consider that the high risk is more similar with all of your diseases, is more similar to active myeloma. By contrast, the low risk is more similar to the MGUS and there are patients that probably do not need treatment. By the selection of the appropriate population, we were able to show that in these patients, in these high-risk patients, in the control arm, the no-treatment arm, the time to progression was 21 months. Eighty-five percent of these patients had already progressed. By contrast, in the lenalidomide-dexamethasone, only 25% of the patients had progressed and the time to progression has not been yet achieved, but what is more important was the analysis of the overall survival. In the no-treatment arm, at 7 g/l, only 64% of the patients are still alive, but in contrast in the interventional arm, at 7 g/l, 95% of the patients continued to be alive, which these demonstrate that early intervention not only influenced the delay to progression but also a significant benefit in overall survival.

Gary Petersen – That's remarkable! That's outstanding! Can you please tell us what the future plans are in process or in the planning stage, which we can expect for early identification and treating smoldering myeloma?

Prof. Jesus San Miguel – Okay. We continue to work in both settings. Its better in more precise identification of the high-risk population. Our goal is just to identify the patients that have high risk of progression interrupting myeloma. We define high risk by a rate of 50% of progression within two years or even better, 70% or 82% risk of progression within the first two years. For these patients, currently, we have decided a new clinical trial called the CESAR trial in which the goal is to evaluate the proportion of patients that can be in sustained immunotherapeutic response at five years and we consider that to be in sustained immunotherapeutic response at five years to be cured and this CESAR trial is based on





induction with KRd, carfilzomib-lenalidomide-dex, then autologous transplant, consolidation again with another two cycles of KRd and maintenance with len-dex for two years and all our expectation or prediction is that half of the patients should achieve this objective, this goal.

Gary Petersen – And this is ultra high risk, huh?

Prof. Jesus San Miguel – No, no, no. This is for high risk and ultra high risk.

Gary Petersen – Okay. Both.

Prof. Jesus San Miguel – We did both, high risk and ultra high risk... and the same. This is very..., this trial has already started. We have recruited total of 30 patients already and a very similar trial has been recently activated in the United States. It is called the ASCENT trial, that includes carfilzomib-len-dex plus daratumumab with the possibility of continuing this treatment or to receive consolidation with autologous transplant, but the sign is very similar.

Gary Petersen – Oh, we are all really excited about this..., the possibility for early intervention in eliminating this crab issue which is something that, you know, affected me, took my kidneys away for a long time and affects a lot of other people as well. If you have just high-risk genetic features and not high risk per, you know, high-risk progression, you know, its a little confusing to me because the high risk means different in smoldering than it does in active myeloma, but if you have high-risk features, meaning the FISH features or genetic profiling, if you have those features, did the LD study show early treatment had any impact on patients with the high-risk cytogenetics?

Prof. Jesus San Miguel – Okay. Unfortunately, when we performed the trial, the len-dex, at that time we had genetic information only in a small fraction of the patients and also you should consider that a proportion of patients with genetic abnormalities in smoldering is relatively small, which is good and..., and you don't want just to..., to induce patients that had this genetic abnormality. Their median time to progression was approximately two years. Again, this is the reason why this high-risk group is also a potential group for treatment intervention, at least within clinical trials. We have not fit in smoldering patients, high-risk smoldering, outside of the clinical trial. All our intervention is within the decided clinical trials. Then, in the CESAR trial, the one that is using carfilzomib-len-dex with a goal of curing was included also in this population.

Gary Petersen - Okay. So, you'll..., you'll get that result in the new trial.

Prof. Jesus San Miguel - We will get these results in the near future.

Gary Petersen – Super! Thank you very much. I am going to turn it over to the rest of the panel and to the..., and Jack, you are up?

Jack Aiello – Thank you and thanks, Dr. San Miguel, for being on this call. Just a kind of follouwp on Gary's last question. Are there other possible treatment modalities for high-risk smoldering myeloma such as treatment based on genetic mutation or the so called attacking the myeloma stem cells, things like that or.. really pretty much confined..., we are looking at the treatments like your trials, was looking at because there is not enough of those mutations or ability to find myeloma.

Prof. Jesus San Miguel – Okay. Okay. Okay. I think targeted therapy, targeted therapy will have a clear bias in the myeloma treatment but not as a single treatment modality. I am very sure why this is is because myeloma is different from other hematological malignancies or other cancer in the way that it is not a monogenic disease. In myeloma, usually there are complex genetic abnormalities and for the reason to use only targeted therapy probably will not work. You will need to combine also other drugs.

Jack Aiello – So, we wouldn't expect, for example, the match trial that NCI is doing to work for myeloma





patients because its really only looking at a single genetic mutation?

Prof. Jesus San Miguel – This is my...., my personal view.....that we should use the..., the..., the new target therapies but in combination.

Jack Aiello – Okay and then I am worried...

Prof. Jesus San Miguel - ... which you should not forget that myeloma has a complexity in the clones. Okay?

Jack Aiello – Yes. Thank you. I was fortunate enough to attend a recent IMWG meeting where you said the definition of a curative treatment is that one-third of patients remain myeloma free for 10 plus years. First, I wanted to clarify, does that include with or without maintenance and then I have a follow up question.

Prof. Jesus San Miguel – Okay. For me, the definition of a corrective treatment, you are right, will be that approximately one-third of the patients remain disease free for 10 years and this should be either with or without maintenance. For me, this is not a problem, but to be disease-free for 10 years will be probably that the patient is cured, but we are thinking the way to think about that because if I if I find that a patient is minimal residual disease negative for continuous five years, probably this patient may be cured as well.

Prof. Jesus San Miguel - Whether or not they are still on maintenance treatment. Is that correct?

Jack Aiello – Okay and just a followup, I know you are a football fan, which we call soccer in the US.

Prof. Jesus San Miguel - Definitely. Yeah.

Prof. Jesus San Miguel – So, I am wondering if you kind of take your analogy of football match being 90 minutes, how many minutes to play before we find a curative treatment for some fraction of myeloma or smoldering myeloma patients?

Prof. Jesus San Migue – I would love it to say that we only need five minutes to find corrective treatment, but unfortunately, I think this is not the right answer and its very difficult, yes, but I would not think that we need 80 minutes of the match, even neither 50 minutes. Let's think about 30 or 40 minutes.

Jack Aiello – So maybe somewhere, a little bit beyond half time.

Prof. Jesus San Miguel - Yeah.

Jack Aiello – Okay.

Prof. Jesus San Miguel – This is my..., my dream at least.

Jack Aiello – Thank you so much. I'll turn it back over to Gary.

Prof. Jesus San Miguel – Okay.

Gary Petersen - Yes. If you... I think Cindy hasn't been able to call in. Cindy, are you online?

Priya Menon – No, Gary. I don't think Cindy is online with us.

Gary Petersen - Okay. All right. Hey, Jack!

Priya Menon – Yelak..., I mean we have to read out her questions.

Gary Petersen - Yes. Jack, could you please ask Yelak's question?





Jack Aiello – I can, Gary, but the way the questions go, I think it would actually be better if you ask Cindy's questions first even though I may...

Gary Petersen – That will do. Okay. All right. Yeah. It was... We just found that apparently she was...., was unfortunately detained. All right. Let me ask Cindy's questions. Dr. San Miguel, high-risk smoldering multiple myeloma is currently being defined as likely to progress to active myeloma in two to three years by defined set of criteria. I have read about two sets of criteria – the Mayo model and the Spanish PETHEMA model. Can you briefly explain these models and..., and are there other ways to define high-risk smoldering multiple myeloma? Is there a current agreed-upon definition of high-risk smoldering multiple myeloma? Are researchers investigating the possibility of treating smoldering multiple myeloma patients that have high-risk genetic features as defined by gene expression profiling or some other molecular profiling test even if they don't fit into the current definition of high-risk smoldering multiple myeloma and I think she snuffed about eight questions into one, but you would try to tackle that?

Prof. Jesus San Miguel - Okay. Let me..., let me try to..., to summarize the answer. First of all, these..., what is the major model? The major model for high risk are those patients that have more than 30 g/l of monoclonal component paraprotein plus more than 10% plasma cells in the bone marrow. The Spanish criteria in dependency of the proportion of plasma cell and dependency of the amount of paraprotein included as a criteria that they should have either more than 30, the Spanish criteria is either more than 30 or more than 10% plasma cell and in addition to one of these two criteria, all the plasma cells should be clonal and the patient should have immunoparesis. Okay. There are other criteria to predict also high risk such as an evolving pattern of evolution. This means that a component is increasing month after month or the presence of high risk cytogenetics or the presence of a high-risk gene expression profiling. These are new criteria that also present with high risk of progression and the next question is, will we agree of the definition of high risk. You don't need to have one single classification for high risk and in fact, you should have several different criteria as the ones that I am mentioning. This means that they are dependent criteria and all of them qualify for high risk. Its the same in active myeloma, if you have high-risk cytogenetics, you have inactive myeloma already, poor progress, but if you have extramedullary disease, it is also poor prognosis. If you have stage III plus elevated LDH, its is poor prognosis. I mean these are independent factors and all of them qualify for poor prognosis in the context of active myeloma. The same occurs if there is smoldering. There are several..., several different factors that help identify the high risk and this is not a bad, this is a good news just to have the different opportunities to identify this patient and not only a single marker. In other words, you have several volume markers that can contribute and help you. And the final question is..., was whether or not there are clinical trials that will investigate the value of having intervention according to gene expression profiling or other molecular profiling, but sure there are going to be clinical trials in this context.

Gary Petersen – Okay. Thank you so much, doctor. How did you select the treatment protocol in the CESAR trial?

Prof. Jesus San Miguel – Okay. The treatment protocol was decided in the CESAR trial with a goal, to try to cure half of the high-risk smoldering patients. For this reason, we decided at that time, it was almost 2 years ago, to combine the most active drugs, one potential drug that moment was that we consider carfilzomib, would be probably the most active one. One …lenalidomide plus dexamethasone plus the autologous transplant and also consolidation and then maintenance. Our goal was just to…, to try to combine the most active drugs available at that time, that time monoclonal antibodies were not available.

Gary Petersen – Okay. All right. Yeah. So, high-dose therapy followed by autologous stem cell transplantation... Okay. So, they also will be getting melphalan during this CESAR trial, correct?

Prof. Jesus San Miguel – Yeah. Yeah. I mean, in fact, we decided, okay, what is the optimal treatment in active myeloma in patients that have graft symptoms and it was the three combination that offered proteasome inhibitor, IMiD, and we chose six cycles of carfilzomib, lenalidomide and low-dose dexamethasone. We had stem cell collection after the third cycle and then two more after the completion of





the six cycles into high-dose melphalan, then the consolidation with another two cycles of KRd, carfilzomiblenalidomide-dex. This consolidation was given three months..., is given three months after the transplant and then two years' maintenance with len/dex.

Gary Petersen – Okay. So, the last one is, besides CESAR and ASCENT trials, are there any other things that are on the horizon for high-risk smoldering multiple myeloma?

Prof. Jesus San Miguel – Yeah, there are several other trials with different drug combinations that are being tested also with either lenalidomide alone, also with carfilzomib, lenalidomide and dex without autologous transplant, also with elotuzumab in smoldering patients and also with monoclonal antibodies as a single agent.

Gary Petersen – Okay. Fantastic! Jack, would you like to go over Yelak's questions now?

Jack Aiello – Sure. I know Dr. San Miguel that you know Yelak Biru and he is very sad that he couldn't make the call. Last night, he got called away to a different project, so he asked me to ask his questions of you. Before I get to that, can you explain in the CESAR trial, when MRD testing is done?

Prof. Jesus San Miguel – Okay. In the CESAR trial, the MRD is investigated after induction, after autologous transplant, after consolidation, and during maintenance once a year.

Jack Aiello - Right. And that's all via the flow cytometry method?

Prof. Jesus San Miguel – We are doing both, flow cytometry and sequencing, both.

Jack Aiello – That's fantastic! So, Yelak first asked the following. As we eagerly anticipate the start of the ASCENT trial in the US, can you tell us how your trial is going in Spain and Europe and how its different or how its similar to the ASCENT trial in the US?

Prof. Jesus San Miguel – Okay. The CESAR trial is going pretty well. We have enrolled over 30 patients already and the difference between the CESAR and the ASCENT trial is mainly that the ASCENT trial includes daratumumab as part of induction and consolidation and also as part of the maintenance, then a monoclonal antibody is included. This is the major difference. The second difference is that not all patients will receive autologous transplant, only the candidates are going to receive it or ones that will be able to receive consolidation with autologous, which is then the two major differences.

Jack Aiello – And are you expecting to..., maybe the question is, when are you expecting to be able to announce some results from the CESAR trial?

Prof. Jesus San Miguel - Okay. Not before two years. Because I don't have any results.

Jack Aiello - Yeah. So, 2018 probably. Okay.

Prof. Jesus San Miguel - Yeah.

Jack Aiello – And then Yelak asks, using either or both of these cure trials, you may be able to achieve sustained MRD in some percentage of patients and that's a big deal and could potentially be a paradigm shifting for them. Can you talk about potentially curing subsets of high-risk smoldering myeloma patients and how can we give potentially better treatment and outcomes to those who already have myeloma?

Prof. Jesus San Miguel – Okay. I think our goal at least in the Spanish trial was to achieve cure, in other words to maintain an MRD-negative status in half of the patients, which is our goal. This is an ambitious goal, but probably if we are able to achieve this, this would mean that we are able to cure a substantial proportion of patients by the early intervention.



Jack Aiello – Okay and his final question is, a question that all myeloma patients want to know about, that is, how is the development of blood-based MR testing..., MRD testing going and you see it supplementing bone marrow biopsy-based testing in the next, let's say, one to two years?

Prof. Jesus San Miguel – Okay. I don't think MRD in peripheral blood will be an easy task. I don't think it would be an easy task and the reason is because the myeloma disease is mainly focusing in the bone marrow and blood test happened to have a lot of value for investigation and diagnosis when you have both the diseases, but at the time of minimal residual disease, you need to go to the source of the disease, that is the bone marrow. Then although its a bit painful, at the same time is the best reservoir for the malignant cells and I think you need to focus on the bone marrow. This is my personal feeling.

Jack Aiello – Okay. Well, thank you very much.

Prof. Jesus San Miguel - We are working..., we are working on the peripheral blood, but...

Jack Aiello – Yeah.

Prof. Jesus San Miguel – ... I am not sure that is going to be the best. Okay.

Jack Aiello – Okay. Thank you. Gary, those were Yelak's questions.

Gary Petersen – Okay. Fantastic! Priya, could you see if there are any callers on line who would like to ask Dr. San Miguel any questions?

Priya Menon – Yes, Gary. I think we have Dana on line. Dana?

Dana - Yes. Hi, Priya! Hi, Gary! Yes. Thank you so very much.

Gary Petersen - Hi, Dana!

Dana – Good afternoon, Dr. San Miguel. Thank you so much for taking time out of your day to help smoldering patients understand what is going on in our world. Appreciate it so much. I am listening closely and I am detecting that it makes apparently early intervention makes the most sense before mutational changes take place. Am I right with..., with thinking..., hearing that from you?

Prof. Jesus San Miguel – Okay. Unfortunately, mutational changes are already present frequently at the time of smoldering disease, but..., but my personal position is that this mutation will accumulate with time and for the reason I think is clear rationale for that intervention, to avoid accumulation of mutations.

Dana – Okay. So, with that in mind, as a smoldering patient, how would I go about or would my specialist go about to detect and identify whether any advance mutational changes which make it more challenging or less likely to potentially cure the disease, in other words, how do I know that I have been evaluated early enough in the disease to benefit from either your CESAR trial or the ASCENT trial?

Prof. Jesus San Miguel – We are doing.... Even in the CESAR trial and I suppose in the ASCENT, they are doing the same. We are doing a lot of genomic analysis and probably the answer to your question will come later on when we do this analysis and we expect to evaluate the impact of the different mutational pattern in the outcome of the patients.

Dana – Okay. So, this is... That's one of the answers or one of the questions that you are looking to answer.

Prof. Jesus San Miguel – Yeah. Yeah.

Dana - Yeah and did you also state, Dr. San Miguel, that if we see five years of MRD negativity that that





potentially could be considered a cure for a subset of patients?

Prof. Jesus San Miguel – Yeah. Yeah.

Dana - The five-year mark?

Prof. Jesus San Miguel – Yeah and I think.... I think if you are MRD negative for five consecutive years, the chances to be cured are very high. These will be probably better predictor of outcome than 10 years of completion this year, what was in the past what we consider as potentially cured.

Dana - Okay. So, the..., the CESAR trial doesn't have the daratumumab arm to it, but it does...

Prof. Jesus San Miguel – No. When we decided..., when we decided the daratumumab was not available.

Dana – Right, but it has the KRd part of it...and I am thinking of Dr. Van Green's NIH trial where he just did the KRd without stem cell transplants and it was a.....small group of patients, but some of them actually are maintaining their MRD-negative status for about three years now and they have done it without stem cell transplant. So, I guess my question is, what benefit do you see the stem cell transplant bringing to that KRd treatment protocol?

Prof. Jesus San Miguel – Let..., let..., let me ask you..., let me tell you another question or an... With len/dex, without carfilzomib, we have also patients that maintain a continuous complete remission now for five years, okay, without the carfilzomib. Then, the question is, do we need carfilzomib? No. My answer is yes. We need carfilzomib because we will increase the proportion of patients that are going to be MRD negative and this is the reason why you also implemented autologous transplant, just to increase, to give more chances to the patients to achieve an MRD-negative status.

Dana – Oh, I see.

Prof. Jesus San Miguel – I know that some patients may not need, but we are increasing the chances to many patients...

Dana – I see.

Prof. Jesus San Miguel – ...and this is similar to..., this is similar to what occurred in the past with acute lymphoblastic leukemia. The initial combination of treatment was probably a bit aggressive in the way that we used too many drugs, but we were either to... To demonstrate that we are..., we have the capacity to cure childhood acute lymphoblastic leukemia and from the protocol of curing, we start to identify those patients that probably do not need so much treatment, but for this, you need to establish the protocol of curing.

Dana – I understand that. Thank you! And, Dr. San Miguel, why carfilzomib versus Velcade? Does it have anything to do with carfilzomib is an irreversible proteasome inhibitor and I and not even sure what that means?

Prof. Jesus San Miguel – Not really. Not really. The reason why we chose carfilzomib is because there is a trial in which carfilzomib-dex has been compared with bortezomib-dex in relapsing patients and the responses and the duration of the responses were longer with carfilzomib. For this reason, we decided to choose what was apparently the most effective proteasome inhibitor at least from that trial.

Dana – Okay. Are there any concerns about cardiotoxicity using it? How will the cardiac affect the monitor during your trial?

Prof. Jesus San Miguel – Okay. I mean we do take control for cardiac toxicity, but the proportion of patients that have cardiac problem in..., in the relapse setting and the upfront setting, I am talking about the last





clinical trial on this part and then focused trial with carfilzomib. The proportion is about 3%, 5%, not more than that.

Dana – Oh, okay. So, its..., its..., its very small. So, there really is not a big concern about that. So, a smoldering patient not knowing which way to turn, do I do such an aggressive trial? Do I stand back and..., and wait for something perhaps to see if the daratumumab trials are going to be, you know, the key to the cure. What guidance would you give to a smoldering patient coming into your office for the first time?

Prof. Jesus San Miguel – Okay. Okay. When I have a patient with smoldering, first of all, I try to identify the risk factors. If he is low or intermediate risk, I say, look, you have low chances to progress into active myeloma, then I will delay treatment because their sizes can evolve rapidly and before you develop an active myeloma, probably we may have the most adequate treatment for you in case you need it, then wait because you don't need. You have low risk. If you have high risk, you have at least 50% chances to progress into active myeloma in two years and we have already one clinical trial showing a significant benefit in order of survival, a clear benefit, and we have updated information, the data that will be published very soon in Lancet Oncology in which we demonstrate that there is a clear overall survival benefit, then if that is selective and if there is a clinical trial in your country, your institution, I will seriously consider yes to have early treatment and if I would say in a smoldering patient, I will go for treatment.

Dana – Dr. San Miguel, thank you so very much for taking all of my questions.

Prof. Jesus San Miguel - Pleasure.

Dana – And I appreciate it very much and I appreciate even more so what you are doing for the smoldering myeloma patient population to try to find us some answers because we live in that awful grave, waiting and watching every area. So, thank you for that.

Priya Menon - Thank you, Dana.

Gary Petersen – Thank you, Dana, for some interesting questions.

Gary Petersen – Doctor, one thing that you have mentioned earlier and I just wanted to make sure that I got that correct is, I asked about high-risk genetic features and you mentioned that most of the smoldering patients, whether they are high risk or low risk, haven't developed those features as yet. Was that my....

Prof. Jesus San Miguel – Yes, that's correct. That's correct. And even..., and even..., and even in the MGUS patients, most of the genetic features that we have identified in the multiple myeloma are already present in MGUS patients, but probably they are present in various small clones, without the capacity to progress because this is well controlled by the immune system. Then, our personal feeling is that the genetics..., the genetic difference between MGUS or the smoldering and multiple myeloma is not only that a new genetic abnormality is emerging, that probably this is the case, but also that this is an accumulation or proliferative advantage of one of the clauses that this was already present from the beginning.

Gary Petersen – Okay and I guess few of that MGUS or smoldering, you know, cells, you wouldn't find 4;14 or, you know....

Prof. Jesus San Miguel – There are patients with 4;14, with MGUS with 4;14 that have not progressed for years and years, then genetic is not the only explanation. You need more explanation for the progression.

Gary Petersen – Okay.

Prof. Jesus San Miguel – And I think the resistance is critical.

Gary Petersen – It sounds like, you know, you got to nip in the bud type of thing if you get it early and





that's..., and that's really what we are so strong about this whole process that you are going through and the next feature that we have on this program is not that..., not that we know we can have an impact, I just find it and so we will be talking about the iSTOPMM program and wonder what your thoughts were about that program.

Prof. Jesus San Miguel – I think it is a very effective program and it deserves a lot of research and investment on that.

Gary Petersen – Yeah. All right. I think so as well and I... And again, thank you so much, Dr. San Miguel. Its obvious that...

Prof. Jesus San Miguel – It has been a pleasure.

Gary Petersen – ...from talking to you that you are just one remarkable...., remarkable individual. So, Priya, want to close it up?

Priya Menon – Yeah. Thank you, Gary. Yes. Its almost time and I guess doctor wants to, you know, wrap this up quickly. Thank you, Prof. San Miguel, for your time. This, I think, was a very brilliant talk we shared.

Prof. Jesus San Miguel – Thanks to everybody.

Priya Menon – Thanks for sharing all this information. Gary and Jack, thanks so much for your participation.

Prof. Jesus San Miguel – Okay. Thank you very much.

Priya Menon – Transcript will be available on CureTalks' website. In the last and the third session of highrisk smoldering myeloma, we are talking to Dr. Kristinsson on iSTOPMM treatment on September 14th, so please visit us, curetalks.com, for more details on upcoming shows. Thank you very much.

Prof. Jesus San Miguel – Bye bye.

Priya Menon – Bye bye.

Gary Petersen - Thank you, doctor. Bye bye.