Latest Advances in Myeloma Treatment: ASCO and EHA 2018 Highlights

The treatment field of Multiple Myeloma continues to move forward as novel agents and treatment combinations expand. Whether you are standard risk patient or belong to high-risk group, treatment paradigms are getting better. We are talking to Dr. Mateos on Myeloma research and treatment modalities discussed and presented at the recently concluded American Society of Clinical Oncology (ASCO) and European Hematology Association (EHA) annual meetings.

Full Transcript:

Priya Menon: Welcome to Cure Talks. This is Priya Menon, your host and a very good morning to all joining us from the US and a very good afternoon to those joining us from Europe. Today we are talking about multiple Myeloma. The treatment field of Myeloma continues to move forward as novel agents and treatment combinations expand. Whether you are a standard risk patient or belong to high risk group, treatment paradigms are certainly getting better. Our featured expert for today's show is Dr Maria Victoria Mateos and she'll be talking to us about myeloma research and treatment modalities discussed and presented at the recently concluded American Society of Clinical Oncology and European Hematology Association annual meeting, She is joining us from Spain. A very warm welcome Dr Maria.

Dr Maria Victoria Mateos: Thank you very much. It's really a pleasure for me to be here with you.

Priya: On the panel today are myeloma advocates and survivors, Gary Peterson who is also co-host for this talk, Jack Aiello, Yelak Biru and Matt Goldman. Welcome to Cure Talks everyone, I will hand over to Gary to begin with the discussion Gary, you are on.

Gary Petersen: Okay, well thank you. Well, first I would like to say thank you so much, Maria, for all the work that you've done to prove that if you treat myeloma early, you improve results and have a better overall survival and event free survival. So that was kind of the Rosetta stone that opened and was the key and open the door to the possibility of early treatment and cure. So I think it's amazing what you've done. I can't tell you how pleased I am with the direction that you're taking with Dr Irene Ghobrial and in all kinds of other people to eliminate this and nip it in the bud. But first let's talk about Maria, Dr Maria Victoria Mateos received her medical degree from the University of Valladolid in Spain and completed her residency in hematology at University Hospital of Salamanca, where she completed her doctor degree. She is a consultant physician of Hematology Department and associate professor of Medicine at the University of Salamanca, Spain. In addition, she is the director of the Myeloma program and coordinates the clinical trials unit in Salamanca University Hospital Medical department. Now I would say what she's part of, but I don't need to. I'll just say she is part of pretty much everything, the myeloma working group, international myeloma society and she serves on the European hematology…I mean it goes on and on and on. It's amazing what she's doing. She must be cloned because there's got to be more than one. Dr Mateos has published over 140 papers in her spare time and peer reviewed international journals, some of which had been become key references in multiple myeloma field. She is the associate editor of Myeloma in the Annals of Hematology and a reviewer for journals such as New England Journal of Medicine, Lancet and the Lancet Oncology. So given that I'd say, and all the work that you've been doing that you are one of the top Myeloma specialists in the world. So thank you so much for being with us today and for helping us understand those patients, to understand more of what's going on with the Myeloma treatment, etc. Now, first of all, if you might, like Priya said, could you give us what your key takeaways are from the American Society of Hematology meeting and the European Hematology Association? What are the top most important elements that you took away from that?

Dr Maria Victoria Mateos: Thanks for the invitation and thanks for the kind introduction. So I would like to start by doing an update for the most relevant data from the European Hematology Association and the American Society of Clinical Oncology meeting. But of course after brief presentation, we can discuss about the differences you want to discuss about smoldering myeloma because so no specific answer. That's the only last thing during this last congress. I would like to start by newly diagnosed myeloma patients. And I would like to start by the transplant eligible newly diagnosed myeloma patients and so we know that according to the European guidelines but also according to the American guidelines, so when we consider that the any specific patient is eligible for autologous stem cell transplantation. These patients have to receive an induction, usually based on Cyclophosphamide, Thalidomide, Dexamethasone, Dexamethasone mainly in the US followed by transplant basically maintenance with Lenalidomide. This scheme, the last year association meeting the italian myeloma group presented an update of a phase III trial that they conducted many years ago in which almost 500 newly diagnosed myeloma patients received this induction with BTD – Bortezomib Thalidomide and Dexamethasone followed by planned transplant followed by two additional cycles of consolidation with the BTD and maintenance with Dexamethasone alone. And it seems interesting from this trial, at least from my point of view that we can follow up right now what we didn't know, 10 years so 124 months, so approximately 10 years of medium follow up for these patients and it's important to see, like the medium progression for survival is proportionately 5 years after BTD induction transplant and in transplant and CTD consolidation which I consider is remarkable. But also its important to note too that there is approx 35% of patients that remain alive without progression after 10 years, what is interesting is that to try to evaluate the baseline characteristics of these 34% of patients, who remain alive for so many years we noticed and decided to establish the baseline characteristics and maybe relate to genomic. To be specific a group of patients with extremely good, in terms of overall survival. I see that it's also very remarkable to say that 60% of the patients remain alive at the same year. And I see that this is a proof of concept that the base combination are clearly are increasing the survival for our patients with multiple myeloma. This is remarkable and I would like to remark that in this study, patients could stand the autologous transplantation. So maybe, the role of transplant has to be researched again and has to be made clear again. In this current event we are essentially discussing about the role of transplant in the follow up setting, single transplant, so the patients can avoid the transplant in the after all setting. But, I think that this study with a longer follow in spite of the use of standard transplant I think the results are very remarkable.

Another interesting presentation in which we move forward to the second generation progression, also by the Italian myeloma group. Patients received induction with Bortezomib in combination with Cyclophosphamide and Dexamethasone or in combination with Lenalidomide and Dexamethasone. So in this presentation, main focus is only on the efficacy after the induction, with 4 cycles of Calfilzomib, Cyclo, Dex versus Carfilzomib Lenalidomide and Dexamethasone. …(unlcear) Calfilzomib Lenalidomide and Dexamethasone is better than Calfilzomib, Cyclophosphamide and Dexamethasone (unlcear)…from 94 versus 86%, but most importantly when we evaluated the responses of high quality. 33% patients achieve complete response after 4 induction cycles with KRD versus 21% of patients achieved CR with Carfilzomib, Cyclophosphamide and Dexamethasone. And minimum residual disease was also evaluated and again …(unclear) a significantly higher proportion of patients achieved MRD negative, when they received the Carfilzomib with Lenalidomide and Dexamethasone. So I think KRd can potentially be a new standard of review as part of induction in these young, newly diagnosed myeloma patients before autologous transplantation. I mean in the future KRd can be a conventional induction, and also formally available to patients for autologous transplantation.

Another interesting update at the European Hematology Association meeting, focussed on the newly diagnosed myeloma patients, candidates for autologous transplantation, was European myeloma network trial, a large trial, that included it was trying to do more than 1000 newly diagnosed myeloma patients. Even today we see the induction with CyBorD 3-4 cycles. And patients were randomised to who might want to receive consolidation with VMP vs Melphalan followed by autologous SC transplantation. And after these first consolidation patients were randomized again to receive a consolidation with 2 cycles of VRd – Bortezomib Lenalidomide and Dexamethasone with no consolidation. Consolidation with VRd was superior to no consolidation in terms of survival, although its did have any benefits in overall survival. I haven't pursued what I was saying at the Congress Consortium newly diagnosed myeloma patients eligible for ASC transplantation I would summarise, is it possible to ASC transplantation at relapse. We know that here in

Europe, transplant continues to be the standard of care. However, probably in my personal opinion, I think that the absence of benefit in over survival makes possible to consider some patients for and I consider, in the future, minimal residual disease status will be incorporated into the algorithm but its possible for patients receiving an optimal induction with combination or 3 + monoclonal antibodies, if they achieved minimal residual disease negative, maybe they can try the patients, need not proceed to 12 transplantation so we can potentially reserve the transplant for relapse.

Gary: When do you think that might happen? You know, when you get the clinical trial data that proves that and couldn't get it approved by the European commission or whatever you have there?

Dr Maria Victoria Mateos: So I don't know. Maybe five years but really I don't know. This is a personal opinion because in order to prove this I think that we would need to conduct a big trial so patients can receive imagine – VRd plus series of 8 monoclonal antibodies or KRd plus series of 8 monoclonal antibodies, imagine 6 induction cycles and patients achieving MRD negative after 6 induction cycles. So the optimal way would be to randomize these patients with MRD negative to receive transplant or no transplant. And I …….that the outcomes of patients with MRD will be equivalent, if they receive the autologous transplantation. I don't personally know if the trial is going to be done because maybe the number of patients required to answer this question would be more than 100 or 2000 patients. But I think that this is my personal opinion, if you consider the outcome of patients with MRD negative in the French study after VRD induction followed by ASC transplantation, they evaluated the MRD before maintenance… and the patients with MRD negative, the outcome is equivalent if they received or not transplantation. This is the rationale for the answer to this question, at least from my personal point of view.

Gary: Very very interesting and very good.

Dr Maria Victoria Mateos: No, the question number two for me, what is the role of consolidation right now on? A big question, the answer to this question is for me is I don't to know. Maybe further analysis are required, especially starting a trial conducted in the United States, but my personal opinion is that a newly diagnosed myeloma patients receive an optimal induction with Proteazomib and Imidz, maybe a monoclonal antibodies, and they receive an optimal response, maybe consolidation is not necessary and they can proceed to receive maintenance. My rational for this this answer is when we go to a standard trials, so consolidation versus no consolidation or take a transplantation are equivalent. Induction with most patients receive Bortezomib, Lenalidomide and Dexamethasone and in fact all patients receive Lenalidomide. Again further analysis is required, but this is my personal point of view about consolidation and effect my clinical practice, I used to evaluate the response after transplantation, three months after transplant, and the minimum residual disease is negative, patients do not receive the consolidation and they go by maintenance therapy. However, if the MRD is positive, they do not achieve complete response, they require the consolidation in order to try to improve the quality of the response before moving to maintenance.

Gary: One thing I found in the difference between Europe and the United States is that you use autologous transplant much more than we do in the United States. Do you know what that difference is and why there is such a difference?

Dr Maria Victoria Mateos: Yeah, I think the approach is completely different because in Europe you know that are the high ability between the optimal induction which is not so wide like in US. So from my point of view transplant is an excellent complimentary strategy after induction with 3 drug combinations but maybe it's in line with my answer to my previous question. Maybe we are able to use optimal induction. We are monoclonal antibodies not only during 3 or 4 cycles but 6 or even 8 cycles, maybe we can avoid autologous transplantation but in countries or in hospitals or in regions we think the availability for optimal induction is not possible. So in these specific situations, I think that autologous transplantation is able to improve the quality of response and patients are able to receive the high dose melphalan and melphalan is very effective for the treatment of patients with multiple myeloma. So this is the but again this is a personal opinion, if you ask hematologists, they would say that transplant remains the standard of care. And I have to say that here in Spain we continue doing that but we can envision that in the future, maybe we can have more autologous

transplantation in unspecific suitable patients because something that I am seeing everyday with my patients in the clinic is that when they are receiving induction with VRd, they are perfect and they perform this fine and they are able do daily activities without any problem. The first moment in which they really feel like patient with severe illness is during autologous transplantation. So we make it possible at least my personal opinion about the possibility of consolidation in the future with optimally inductions plus monoclonal antibodies and achieving an optimal response.

Gary: Yeah, I think what we'll do is we'll start to go to the question. And the first question, doctor is that I have been, frankly very, very impressed with your work on high risk smoldering multiple myeloma and there's also a couple of people who will be calling in later that are also very interested because they are smoldering patients. There is a hypothesis if you're treating myeloma early, patients will live longer and maybe cured. Your work has been instrumental in answering this question. Can you give us an update on your work and other research on this subject?

Dr Maria Victoria Mateos: Yeah, of course. I can do it. So you know that the important concept to realize in smoldering myeloma is Iatrogenicity. Smoldering means to have a monoclonal component higher than 3g per deciliter and all between 10 and 50% of plasma cell without any myeloma cells. We can find patients who have low risk of progression to myeloma, patients on intermediate risk of progression to myeloma; patients at high risk to myeloma. When we evaluate the risk of patients to myeloma, so patients have low risk, the risk is 1% a year so the patients have monoclonal, patients with intermediate risk of myeloma, the risk is approx 3% a year and patients with high risk, they are a group of patients whose risk is approximately 10% a year. What is the first important concept – reduce the diagnosis of smoldering, we have to try and identify and explain to our patient what is the risk of progression to myeloma is, because if the patient has low risk of progression to myeloma so we can say OK you are not going to have any problem and you can become confident because the risk of the patient is risk of the patient is very low.

Even if the risk of the patient is intermediate, we can plan follow up every 6 months probably in the first year. We know the path of progression is monoclonal component, but if the risk of progression is 10% per year, if the risk of myeloma is high, maybe the information we have at this stage of the patient is completely different and we can potentially plan the treatment. And the first question, we can get from the patient is it possible to identify the risk of progression to myeloma and the answer has to be yes, we can and we know that there are different divisions in order to evaluate the risk of progression to myeloma. But there are 2 big models. One is by Mayoclinic and the other by Spanish Myeloma Global but there are simple and most importantly validated in the clinical trials. According to Mayo, all the smoldering myeloma patients with more 3 times the monoclonal components, plus more content in plasma concentration. The risk of progression to myeloma is 60% per year, in another words the risk of progression to myeloma is approximately 2 years. This model can be optimised by the addition to light chain rate. That was published by the spanish myeloma group. And this is complicated because they tried to evaluate the plasma cell compartment in the bone marrow by flow cytometry. That is very simple, because when you evaluate in the plasma cell compartment which is the proportion of normal plasma cells and malignant plasma cells and it easy to understand the proportion of clonal plasma cells, malignant plasma cells is very high, so higher than 95 percent together they will move, we feel that if the smoldering myeloma is IgG, the IgA and IgM are decreased. In this situation, the risk of progression to myeloma is significantly higher, approximately again 50% of 2 year. In other words median time to progression between years. These are the 2 models we validated in clinical trial, although it is possible to evaluate the risk of progression to myeloma using the evolving pattern of the monoclonal component, we can consider the cytogenic abnormality, gene expression profiling etc.

How are we going to harmonize all these different models. We already know the International Myeloma convention is supporting a project, in defining history of smoldering myeloma and developing a new education system. And the idea is to gather data coming from a smoldering myeloma patient in order to develop a simple score model in order to identify the risk of progression to myeloma. Anyway, medical doctors have to evaluate the risk of progression to myeloma. The Spanish myeloma group, published this some years ago the first patient was drawn in 2013, in which we planned, the first time every treatment in high risk smoldering myeloma patients. At the moment the group decided to conduct this study, the standard

of care was no treatment. 125 patients were included in the trial. Half the patients received early treatment with Lenalidomide and Dexamethasone. Half patients did not receive any treatment. Primary endpoint of the study was time to progression to myeloma. So the early treatment with Linalidomide and Dexamethasone, would lead to significantly lower time to progression to myeloma. So the primary endpoint of the trial was met. But it was much more relevant for the benefit with regard to overall survival. It is important to note that this study was published in 2014, and the median follow up was approximately 40 months. And in this study most updated was, median follow up was higher than 6 years (unclear)… and benefit even more evident in terms of overall survival.

It was indeed very good, we were happy to collect only grade 1 and grade 2 adverse events. So very few patients developed adverse events. I think this is the starting point to investigating more and more really interesting population high risk smoldering myeloma patients. In fact, if we go to clinicaltrials.gov, we can see more than 50 clinical trials currently ongoing in this specific population, high risk smoldering myeloma. The most of the clinical trials now ongoing are planned to delay the progression to myeloma, but there are at least 2 important trials in which the objective is to plan the cure. The first one is done by International Myeloma Foundation and the principal investigator Shaji Kumar. The second approach is by the Spanish Myeloma group. And the Spanish Myeloma group plan is, accurate option for how risk smoldering, because in our previous study we proved that any treatment is a wide approach therapy for high risk smoldering myeloma. So we decided move forward in order to plan for this patient population. We selected 90 patients, 90 high risk smoldering myeloma patients. So we planned induction with Carfilzomib, Lenalidomide and Dexamethasone followed by autologous SC transplantation and consolidation and maintenance. So the recruitment of these patients was completed approximately 1 year ago and the preliminary results were shared at last ASH meeting.

I can summarise by saying that after induction, the CR rate was approximately 50% , the CR was 60% after transplant and 74% after consolidation. But the primary point was to evaluate the MRD negative in bone marrow by flow cytometry – Next Generation Flow. And I can say that after consolidation, 62% of patients are MRD negative. The progression for overall survival are encouraging, medium follow up is very short, and we have to wait for a long term for wrap up. We are going to update this data. Right now we are waiting to prepare another abstract so to share at next ASH meeting. But our idea is to the cure high risk smoldering myeloma. And one important question is how can we define a cure because we know that there is not any specific definition for curing multiple myeloma. So we studied, we decided to evaluate the proportion of patients potentially cured and MRD negative sustained after the end of the therapy. So we evaluated a proportion of patients who achieved sustainable MRD negative at 5 years and we can potentially consider that these patients will be potentially cured. This is the research so we are working right now for smoldering although we can imagine that we are thinking about new approaches in the clinical trials for these patients.

Gary: Well, that's really fantastic. Thank you so much. If we can move on now, I'll Jack Aiello, are you online?

Jack Aiello: Hi, I am.. Gary. Thanks for asking. Dr V it's a pleasure to talk with you on the phone. I wanted to ask actually about the prevention of multiple myeloma. I've heard it discussed where we can target high risk MGUS and I'm wondering if you can explain how a patient knows if their MGUS is high risk?

Dr Maria Victoria Mateos: Yeah. So this is also interesting question and I will answer to the best I can. We all know that monoclonal gammopathy is defined by the percent of monoclonal components in 50g and plasma cell situation inferior to 10% without any myeloma defined in it. Overall in relation to myeloma in gram percent per year but its possible to try to identify the specific group of patients within patients with monoclonal gammopathy. And again, the main clinic group decided risk model in order to well identify the risk of progression to myeloma patients within that considering the type of monoclonal antibodies, so IgG vs IgA vs IgM. The size of the monoclonal component and cutoff would be 1.5 g per dl. So they are able to identify a group of patients with high risk of progression to myeloma when the M component is IgA or IgM, when the size of the monoclonal component is superior to 1.5g per dl and when the change ratios are abnormal. And in this case, we can define the group of patients with monoclonal gammopathy can consider

that they are at high risk. So my personal point of view is the risk is always very very below and we can say that a patient has high risk of progression to myeloma, a patient with MGUS at high risk means that maybe 60% of risk of progression at 15 or 20 years. For me, this means always under the risk of progression to myeloma and this is directionwise when we have learned at ASH that monoclonal gammopathy that we are able to say ok you are an MGUS at high risk of progression to myeloma we have to realise that the high risk is between brackets because 15 or 20% of progression of myeloma at 15 years I think that is a very low risk. Specially, this information would be relevant if the patient is having prone to MGUS is 30 years or 40 years. But if the patient is 60 years so, for me the stratification according to the age is not relevant because maybe the patient is going to die from other different disease than monoclonal gammopathy progressing to multiple myeloma. So I think this information is irrelevant if we have the patient in front of us and usually patients are coming to our clinic and they are conscious and consult hematologist because they have potentially a blood card so I think we have to put the information on the table and explain to them very well that they have to be prepared. And if it's not the case, it is better to say that they have to be confident and you have to live your life as you did not have any disease otherwise they create lot of anxiety in some patients.

Jack: Thank you. I'll ask one other question. I have a patient friend who was diagnosed back in 97 and had a stem cell transplant in 98 and was in a complete response for 20 years without maintenance and just relapsed this year. How do we know if a patient really is cured?

Dr Maria Victoria Mateos: Yeah, so this is telling me, so this last weekend I had a patient, more or less in the same situation, he was in complete response without maintenance, but same year in without maintenance in complete response. So I think that this is a challenging question because so we can potentially consider that this is another different disease. The disease the patient had 20 years ago, because otherwise we can potentially speculate about it develop a system that can be more and more relevant in our patients and the control of the disease and maybe the immune system of the patient has been optimised, the immune system possibly controlling the minimal residual disease progression in the bone marrow in the patient and due to specific reason that is so we don't know, infections, some situation in which the immune system are being new surveillance so lost and they allowed the small plasma cells in the bone marrow to be expanded and to produce the disease 20 years later what is really challenging because so I think that this is not what we consider and in fact so to these patients in complete response without maintenance for more than 20 years we can say that these patients are cured, this is what I say to my patients but on the other side it proves that we continue with the follow up and we don't say that in my clinic, never said to one patient in my clinic, it is not necessary to send to my clinic anymore so we continue doing evaluations and so we see because for us I think it is very difficult to say you are cured and in fact these patients that you are a percentage cure and my patient last week, the differences in the group of patient where we can consider the patient is cured, this is not true and this means that we have to continue doing a little research and the investigation. In patients who earlier relapse after the hospital probation also in these term of survival, maybe we are able to evaluate the response and we are able to evaluate the minimal residual disease at high considerate level so we cant be completely sure of the eradication of the disease. This is unfortunate but this is the message.

Jack: Thank you very much. Back to you Gary.

Gary: Thank you Jack. I appreciate it. Matt Goldman, are you online?

Matt Goldman: I am online. Thanks Gary. Thank you. Dr. Quick question, if you could talk a little bit about CAR T and if this is really the wave of the future or is CAR T something that's only going to be usable or applicable to certain patients?

Dr Maria Victoria Mateos: Well, an excellent question. I can say that CAR T cells are a very promising and encouraging approach that will be applicable to all patients. I don't know if we have the information we have right know is especially from last ASH conference meeting is that the CAR-T 2121 evaluated in small series of myeloma patients, but hardly completed it, because most patients were refractory to PIE antibodies, first generation, second generation. So there was not any order. And when we go back and when we evaluate

the efficacy of Bortezomib as a single agent, Pomalidomide and dexamethasone; Pomalidomide, Carfilzomib or even daratumumab single agent, in these specific patients population, in all this studies, the overall response rate was approx 40%. The median progression free survival approx four months. With CAR-T cells the situation is completely different. First, because all the patients responded. Second because significant number of persons achieved complete response. MRD is negative in large proportion of patients and most significantly, the progression free survival was significantly longer.

The progression free survival after CAR T cells was approximately 20 years, I know we can say ok this is not a progression free survival but it is a very long one for the patient population for whom the CAR T cell was evaluated. Of course we have more than longer follow up, we needed to evaluate this CAR T cell approach in earlier stage of the disease. In earlier stage of the disease when new disease cell of the patients will be much more preserved and maybe, we can potentially control the disease in almost all patients. And this will result in significantly longer progression to survival. So we know the logistics of the CAR T cell therapy is not simple right now but so I can imagine that if the CAR T cell will be an excellent option of therapy. I think that surgical companies, academia, patients association – all will benefited because they are going to obtain a significant therapy. From my point of view, this is what we will have to do and I think that there is much of clinical research based on CAR T cell and the results were presented at ASH and ASCO, so my point of view its promising,even from sales point of view.

Matt: Yeah. My second question is about Darzalex. What do I know it's still a fairly new drug, but what are you seeing in terms of, because it seems like it's pretty effective and now it's been approved for frontline treatments here. What are we seeing in terms of survival rates with Darzalex?

Dr Maria Victoria Mateos: Yeah, I think that Darzalex development has been so fast, that we are going to now Darzalex in the afternoon setting. So in spite of no more than two years ago, we were speaking about Daratumumab as the first monoclonal antibody for refractory myeloma patients, I think that Daratumumab is going to be used in the afternoon setting. I think that for both transplant and non-transplant eligible, the optimal or standard of care will be 3 drug combination based on progression for secondary…(unclear)…the lenalidomide, dexamethasone plus the monoclonal antibody. And the future of monoclonal antibody can potentially be the Daratumumab and Isatuximab, but as of now there is only one approval of daratumumab in combination with BNP for most myeloma patients. And we also have daratumumab in combination BTP and also in combination with VRd. So, I think the role of Daratumumab will be third line of therapy, it will be possible to treat patients with monoclonal antibodies and we need to prove its possible because if there is not a rate of expression I think it will be difficult to prescribe the monoclonal antibody.

Matt: Okay. Appreciate that. Thanks very much doctor.

Gary: Thank you Matt. Yelak are you on, if you can make your two questions no more than about five minutes, that would be great. So we could have some time for the audience. We got a few questions there from Dana and some others as well.

Yelak Biru: Sure, no problem. Gary, Dr. Mateos. Thank you for all the work you do and for spending the last hour with us. I actually want to double click on Matt's question around the durability of Dara, what are the options for progress while on Dara, what is the role of Elo or Elo-Pom or other salvage regimens and also in the same question, I guess, given these drugs are becoming available early in the disease life cycle, is there an optimal sequencing pattern and that one should aspire for?

Dr Maria Victoria Mateos: Yeah. So concerning your first question, the role of Elo or combination of Elo and Pom. So I think you are completely right. This is in line with your second question regarding optimal sequencing. We have this productive role because we have the first line of therapy because the second line of therapy is going to be clearly influenced by the first line of therapy. So we have to try to prescribe the best to prescribe the best the first for two reasons. The first reason is because we are going to obtain the maximum benefit from the first line of therapy and the second important point is, so we are going to treat our patients and we are going to do those patients therapy so wanted to benefit the most patients so I think we

must select the best the first. And ideally combination of dara+Vrd, for example, would be optimal induction regime for both transplant and non-transplant eligible. How about the relapse? There would be 2 different approaches. One to go to maintain the minimal abrasion and to go to the second generation…, as you said to go to pomalidomide, dexamethasone, maybe in combination to Elotuzumab or, maybe in combination with Bortezomib, if the patient has strength to Bortezomib in the afternoon setting. And the patient receive Bortezomib for a limited period of time, may be superior to other cycles…(unclear)…Pomalidomide, dexamethasone and Bortezomib. Another possibility is first line of therapy is based on Pomalidomide to move to Pomalidomide, Dexamethasone plus carfilzomib. So, second generation proteasome inhibitor with Pomalidomide, Dexamethasone and carfilzomib..is also very active therapy. Another possibility – Pom, Dex plus Cyclophosphamide when Elotuzumab and carfilzomib are not available. Cyclophosphamide at 50 mg daily also has potential immunomodulatory effect, and can potentially be ideal rescue therapy.

Beyond this, Pomalidomide Dexamethasone based combination, I consider that they will be used more and more in first relapse.

So I think that we are going to have a (unclear) may be available very soon to rescue these patients. And we are going to have monoclonal antibodies like BCMA. BCMA, CAR-T cell or dual or bispecific or conjugated monoclonal antibody. I feel that in the near future BCMA will become the third line of therapy, especially in the US because, it is going to be easier to have access to these new agents. But, we don't know, because the BCMA may move to the first relapse or even after 2nd intervention. But I think the landscape of patients with myeloma is so changing almost every year or 2 times per year. After ASH or ASCO every year the landscape is changing.

Yelak: Gary, I'm going to yield my second question to the callers, I think that to have more inclusive and smarter questions on mine.

Gary: No No, that's not true Yelak, the only reason you're last is because your first name starts with a Y.

Yelak: Haha that's ok. You have good questions lined up. So go on. Thanks.

Gary: Thank you Yelak. I truly appreciate that. Priya, could you bring the callers online?

Priya: I think we have Dana Holmes online. Hi Dana.

Dana/Caller 1: Hi Priya. Hi Gary. Thanks so much Dr. Mateos, thank you so much for taking the time out of your busy day to speak to us. Appreciate it very much. I'm a smoldering myeloma patient, so of course I'm very, very interested in the work that you're continuing to do in our patient population and thank you for that. I have a couple of questions and I'm going to start with, in your experience, what are the most important or reliable validated biomarkers to use to assess a smoldering patient's risk to progression. Specifically, what is the significance of circulating plasma cells in a smoldering patient. Does this typically indicate a more aggressive disease biology? Is there a threshold level that becomes more worrisome when they find these circulating plasma cells or does the mere presence of them prompt concern?

Dr Maria Victoria Mateos: Thank you for the questions. So concerning the first question right now for me, the most reliable biomarker, that can establish the risk of progression to myeloma, seems to be the one with the Mayoclinic model. Because they juxtapose the size of the end component, the plasma cell bone marrow filtration, and the Free light chain rate. So they kind of establish the risk of progression to myeloma. But we have to realize that, this model was published in New England Journal of medicine in in 2007, in a series of almost 500 smoldering myeloma patients.

Why I mention this information, because right now, again every other month, if you go to pubmed, you can see specific manuscript or specific paper with immuno diagnostic biomarkers, studying risk of progression to multiple myeloma. But, most of them have small number of patients with not a very long follow up. I think that we have to realise the Mayo clinic risk model is a very well consolidated risk model and I am trying to get it

validated in our next trial. And if you want to add to it – cytogenetic information, gene expression profiling and show – the size of the monoclonal component, the plasma cell bone marrow infiltration, these can identify the risk of progression to myeloma. Another important point which evaluates the pattern of the evolution of the monoclonal component. Because if you see that over time, especially over first six months, the end component increased. And the level (unclear) decreased, So this means that the risk of progression to myeloma is going to be high.

And concerning the second question about circulating plasma cells, so I think that is very interesting. But is under research at the present time. We know that in myeloma and all smoldering myeloma patients, in all of these type of patients with smoldering and myeloma, we can detect circulating plasma cells. But now there is at least in Europe, this project conducted by Spain, France, Italy and Germany – in which we are going to evaluate, especially what you asked me, and how they can the plasma cells in progression to myeloma but the problem is I can say you, this cut off is able to predict high risk of progression to myeloma but now I would prefer to maintain the Mayo Clinic risk model together with the Spanish model.

Caller 1: Okay. Thank you so much for that. And Dr Mateos do your smoldering trials included patients with high risk myeloma biology, in other words, deletion 17 p, the 1q abnormalities? And, are you seeing the same deep response in these patients as you would in a more standard or intermediate risk patient? Someone let's say who has an 11/14 trisomy type of myeloma or smoldering myeloma?

Dr Maria Victoria Mateos: Yeah. Yes. In the first study was conducted, the trial started if I remember well in 2007. So we collect the cytogenetic information but the proportion of patients with high risk cytogenetic abnormality was not very high. At the end we had we had 60 patients with high risk smoldering myeloma treated with Lenalidmide and Dexamethasone and I can say that inspite of the small number of patients there was not any difference in the rate of progression free survival and in the overall survival. But again, the information it has to be considered with caution; as the because the number of patients with 14 deletions was very low. But now in our new trial, we are collecting so much wide cytogenetic information because we are doing not only 4-14 deletions 17p but also mention 1q deletion 1p and even we are doing gene expression profiling as well as next generation sequencing to evaluate the mutational pattern. And choosing how the efficacy, how the response is going to be influenced by the specific abnormality. But now we don't have the research at that moment.

Caller 1: Okay. Is there any emerging data to suggest early treatment may actually lead to aggressive clonal selection, if the given treatment, in other words, would eliminate the clones responsive to that treatment, but could potentially leave the resistive clones behind to further proliferate and mutate. I think that's a concern that I personally have always had and I don't know if it's a valid concern because I do realize, again, this is very early, these are very early studies and no one probably knows and it's probably a question that no one can really answer, but I'm going to pose that to you because it is a concern of mine.

Dr Maria Victoria Mateos: No, I can say, but the answer to your question is no. In our trial, we collected all risk therapy. These involved control and experimental arm. In the control arm all patients have already progressed to myeloma and they received the second line of therapy, the patient was eligible to receive transplant and so on. In the control arm, the patients who relapsed, patients who progressed after Lenalidomide dexamethasone, they received therapy, basically based on also combination, or even conventional chemotherapy, transplant and so on. We evaluated (unclear) ..it was similar in both group of patients. But most importantly we evaluated the overall survival with progression to myeloma. I can say that survival is exactly the same, the early treatment with dexamethasone showed notable result because the patients responded very well to the therapy and survival. And this is what I can say, I don't know if the upcoming trial use any end point that has been evaluated. I think this is the only trial in which this aspect has been so far evaluated.

Caller 1: Okay. Dr. Mateos. Do you see any limitations with MRD testing, specifically sample bias and the heterogeneity of those samples? Would it matter that does the sensitivity of the actual MRD type of testing matter with that?

Dr Maria Victoria Mateos: Yes, so I think that the assessment specifically the MRD assessment is important because, though we don't have any specific database on smoldering although we are evaluating MRD in our trial. And we are able to achieve a sensitivity level of 10 to the minus five and in some patients even 10 to the minus six. Of course based on the sensitivity level, I think that the number of patients going to come to receive MRD negativity is going to be in trivial. But the outcome's going to be more useful for these patients. Probably, these are results that can be extrapolated from the French group also the Spanish myeloma group in newly diagnosed myeloma patients treated with Bortezomib, Lenalidomide and Dexamethasone, MRD by next generation sequencing, where the sensitivity level is approximately 10 to the minus six. The outcome for this specific group of patients is much more better and similar, in both trials using different techniques for the evaluation of MRD. So I think that those assessments are available and it is important and we are able to achieve specificity of 10 to the minus six and it can predict a better outcome.

Caller 1: Okay. And Dr. Mateos, what about liquid biopsies? Do you ever see these actually being a replacement someday for bone marrow biopsies and can these potentially overcome the spatial heterogeneity of sample bias that we see with bone marrow biopsy testing?

Dr Maria Victoria Mateos: So are you asking me about bone marrow biopsy?

Caller 1: The blood biopsies

Dr Maria Victoria Mateos: Ah blood biopsy? Again I think that is is a really very interesting question. But in myeloma I think we have to wait because I think it is not going to be easy. Although we have to investigate, I say that these will be extremely important to avoid the bone marrow aspiration, bone marrow biopsies of the patient. But, we have to investigate and we have to be very confident in order to detect really a disease using just the blood samples. So right now I think it's too early to say that it is possible to do blood biopsies, using blood samples so in terms of a instead story of bone marrow biopsy, say that it is too early.

Gary: Wonderful. I was just wondering, do you have time for one more question? I know we have Bonnie who has called and scheduled a question and would like to have Priya ask it for her. Do you have time for one more question? Dr Mateo?

Priya: Doctor Bonnie wants to know, she says, that she did a piece recently on adapted therapeutic approach and says that approach may not produce lasting missions as well as using less than maximum tolerated dose and building in drug holidays?

Dr Maria Victoria Mateos: So, I think that this theory is associated so right now you know, that almost all options for therapy for myeloma patients are based on I would say, continuous therapy. And so for me it is very difficult to have a patient in front of me and to start maintenance or transplant. And I usually receive the question how long?… I have to say I don't know. As soon as I say ..Until progression… the immediate question from the patient is that, so you are sure that I am going to relapse. I'm not sure. So I think that it's complicated and I completely agree that we have to work on this, what you said the adapted therapeutic approach. It is not reliable, you have in front of me myeloma patients with 40 or 50 years and therapy with lenalidomide as maintenance for 40 years because they think that this is not practice and I think that this is not practical and not going to be possible. On the other side, I think that the approach to therapy for myeloma patients right now is similar what we did many years ago for patients many years ago with acute lymphoblastic leukemia patients. We started with a very aggressive option of therapy with a very intensive option of therapy for all patients and now we are able to adapt the therapy to the patient according to the risk of the disease. And now the transformation of lymphoblastic leukemia patient that received the therapy is much more softer. So I think that this is what we have to do with the patients with myeloma is to make a the plan of individualised therapy, and optimisation of therapy based on risk. And according to your definition to try to establish a plan for each patient and individualise the treatment course.

Priya: Thank you very much Dr Mateos. I think we've taken some extra time, but thank you so very much for the hour you spent with us and all the comprehensive and detailed information that you've shared. Gary,

Jack, Matt and Yelak, thank you so much, those were great questions and thanks for making it in the morning. The talk and the transcript will be available on our website. Please visit curetalks.com for details of upcoming talks. Thank you everyone. Have a nice day. Thank you.