Everything you need to know about Daratumumab and Multiple Myeloma

FDA recently approved daratumumab (Darzalex) to treat patients with multiple myeloma who have received atleast three prior treatments.

Daratumumab is the first monoclonal antibody approved for treating myeloma and provides another treatment option for patients who have become resistant to other therapies.

Our myeloma panel is talking to the father of daratumumab, Dr. Torben Plesner, on the use of this drug in treating multiple myeloma.

Full Transcript:

Funding for this talk comes from TrialX, connecting patients to clinical trials

Priya Menon – Good morning and welcome to the 101st episode of CureTalks. I am Priya Menon, Scientific Media Editor, CureTalks, joining you from India. Its with a very heavy heart that we are here today. Our myeloma panel and myeloma community has lost a dear friend and advocate, Pat Killingsworth. Pat was an integral part of our panel, and he has left behind a vacuum that we are still trying to come to terms with. Dear friend, Pat, you fought a brave battle against myeloma and your efforts in educating people on myeloma are incomparable and more than anything you were a friend to all of us. As our myeloma panel of Gary, Jack, Cynthia, Matt, and Nick say goodbye to you, we realize that now you have passed the baton to us. We will continue your efforts to share information on myeloma and reach out to as many people as we can so that together we can get rid of this dreadful disease. We will miss you, Pat.

Priya Menon – With that note, I would like to start today's talk. We are talking about daratumumab and multiple myeloma. My co-host for the evening is Gary Petersen, editor of myelomasurvival.com. Supporting Gary are experienced myeloma survivors and advocates, Jack Aiello and Cynthia Chmielewski.

Priya Menon – FDA recently approved daratumumab or Darzalex to treat patients with multiple myeloma who have received at least three prior treatments. Daratumumab is the first monoclonal antibody approved for treating myeloma and provides another treatment option for patients who have become resistant to other therapies. We are talking to the father of daratumumab, Dr. Torben Plesner, on the use of this drug in treating multiple myeloma. Dr. Plesner is hematologist in the Department of Hematology in Denmark and Professor at the University of Southern Denmark. Welcome to CureTalks, everyone. Before I hand over to Gary to begin with the discussion, I would like to remind the audience that if you have a question for our

expert, you can post it on CureTalks' website or mail it to priya@trialx.com. If you want to ask your question live, please press 1 on your keypads and let us know. We will bring you on air to ask your question. With that, its over to Gary.

Gary Petersen – Hi! Thank you, Priya, for bringing that nice eulogy for us for Pat. I certainly do appreciate that, and I want to welcome Dr. Plesner on the program. Dr. Plesner happens to be Danish, so god morgen, god eftermiddag, _____[00:03:30]_____, (laughter) which is supposed to mean good morning or for you in Denmark, good afternoon, but my Danish is probably pretty bad. Dr. Plesner happens to be the Head of the Department of Hematology at Vejle Hospital and the Founder of the department's clinical research unit. He is also a lecturer at the University of Southern Denmark and has his medical degree from the University of Copenhagen. He is certified as a clinical chemist, Speciality in Denmark as well as an internal medicine specialist and finally certified as a specialist in hematology in Denmark. He also has over a hundred peer review publications and…, and in his spare time helps to develop first-in-class antibody called daratumumab. So, Dr. Plesner, you are amazing in all that you have done, and we are so thankful that you've come. Dr. Plesner, thank you so much for coming to us. God morgen or god eftermiddag for you!

Dr. Torben Plesner – God morgen! This is afternoon in… Actually, I'm…, I'm having a skiing holiday in Italy. Its afternoon here, but good morning to you.

Gary Petersen – God morgen! I went through your…, your…, your resume or curriculum vitae and you…, its impressive obviously and…, and I think the biggest single thing is the fact that you…, you've brought us a whole new class of drugs in…, in daratumumab or Darzalex and…, and we do appreciate that and we want to learn little bit more about that, you know, for all of our listeners and our listeners generally happen to be, you know, other patients and they in turn aren't necessarily, you know, if you could try to, you know, provide us with kind of a patient-friendly evaluation, but, doctor, for…, you know, thank you for all your great work and…, and maybe you can start by explaining what a monoclonal antibody is and how it works and…, and is this an immunotherapy or can your explain how it differs from immunotherapy?

Dr. Torben Plesner – Its a pleasure speaking to you, Gary, and thank you very much for the kind introduction. Can you hear what I am saying?

Gary Petersen – Yes, yes, very clear. Its very clear.

Dr. Torben Plesner – That's good. That's good. I just wanted to say from the beginning that, you know, as success has many fathers and a fiasco has none. I have been lucky to be involved early in one of the clinical program for daratumumab. So, I could treat the first patients, but definitely the daratumumab or Darzalex has…, has many fathers. You were asking about what is a monoclonal antibody.

Gary Petersen – Yes and how it…

Dr. Torben Plesner – You are still…, you are still with me?

Gary Petersen – Yes, yes.

Dr. Torben Plesner – Yeah.

Gary Petersen – …and…, and how it might differ from immunotherapy or is it immunotherapy?

Dr. Torben Plesner – Yeah. Yeah. I will try to make…, make some points here. An antibody is a molecule that prevents our body from becoming invaded by micro-organisms. Each day we produce many thousand molecules to remain free of disease. These antibodies are polyclonal in nature, meaning that they divide from many different families of immune cells. A monoclonal antibody, in contrast, is derived from a single family of immune cells that has been taken out of an immunized animal and propagated through the culture. The advantages of the monoclonal antibody as opposed to the polyclonal is that it can be produced in

cultures in unlimited amounts. It can be modified chemically to behave as a human molecule that does not elicit unwanted reactions when used for therapy and also the specificity is very well defined so we know which molecule it binds to on a target cell like a cancer cell. These are major advantages of the monoclonal antibody technology that was invented in 1975 by a young German scientist, George Köhler, working with Cesar Milstein in Cambridge, in the United Kingdom. So, there has been a major breakthrough in many aspects of biomedical science. Treating with a monoclonal antibody, that is now possible. It is one way of providing an immunotherapy, and it has already proven to be very successful in the area of lymphoma where cure rates have been substantially improved by combining a monoclonal antibody with chemotherapy.

Gary Petersen – Thank you very much, doctor. That… I know that you have worked with… It was a very… Its a very small German, not German, Danish company…

Dr. Torben Plesner – Danish company, yes, Genmab.

Gary Petersen – Yeah. Yeah. Yeah. It… I was looking and it was…, its Genmab, is that it?

Dr. Torben Plesner – Genmab, yeah.

Gary Petersen – Yeah and its in…, in Copenhagen and….

Dr. Torben Plesner – It has the headquarters in…

Gary Petersen – Yeah?

Dr. Torben Plesner – It has its headquarter in Copenhagen and a very important research and development unit in Utrecht in…., in Holland.

Gary Petersen – Uhmm… Well… I looked in, the sales were 78 million dollars which, you know, it isn't a very large company. So, its really a…, a little company that could and I guess Denmark produced you and daratumumab, so its the little country that could as well.

(Laughter)

Dr. Torben Plesner – So…, so while Genmab has this strategy, they…, they take care of the very early development of monoclonal antibodies and explore in phase 1 and early phase 2 if this looks like an interesting molecule and if so, they make an agreement with either partners to take it into phase…, to expand it in phase 2 and take it into phase 3 clinical trials because Genmab really doesn't have the muscles to do so. So, in the case of daratumumab, they partnered with Janssen which in my opinion was a very good choice because Janssen has a great expertise in…, in multiple myeloma and so it has proven to be a very, very good choice of partner.

Gary Petersen – Okay. Now, its a new class. They call it a new class of drugs and it seems to make all other classes of drugs work better. I remember reading a couple years ago about if you put lenalidomide and dexamethasone and daratumumab in vitro, it worked much better than len/dex. The same thing with VRd and it just seemed like anything that you put it together with, it…, it worked better than they by themselves. So, however…

Dr. Torben Plesner – Its certainly true that…

Gary Petersen – Excuse me?

Dr. Torben Plesner – Its certainly true that the daratumumab is a new class of drugs for treatment of myeloma. You know, we have for decades had alkylating agents, old-fashioned chemotherapy to treat myeloma together with glucocorticosteroids. More recently from mid 2000…. around 2005, we had new

developments with proteasome inhibitors and modern IMiDs, so called IMiDs with lenalidomide and pomalidomide as…, as good examples. So, we had actually four classes of drugs for treatment of myeloma and we have made substantial progress with these new drugs as well, but now the antibodies come on stage as a totally new way of killing myeloma cells and its true to allude to that daratumumab may be combined with any sets of the previously used classes of drugs and its likely to provide additive or synergistic activity with these drugs for killing of myeloma cells.

Gary Petersen – Okay and the last part of my question would be, its right now only approved after three lines of therapy and as a single agent. So, when will we be able to unlock its real potential in this combination treatment that you talked about?

Dr. Torben Plesner – You know phase 3 trials are ongoing for the relapsed refractory setting. Recruitment has been finished and we are waiting for…, for data to emerge. For the frontline setting, daratumumab has moved into the frontline. For the frontline setting, we are still enrolling patients into trials and I would strongly advise patients to…, if possible to…, to enter such trials so we can collect more information and gradually have acceptance from the authorities to move daratumumab from the later stages of multiple myeloma up front where I think it…, it belongs.

Gary Petersen – Well, thank you. CD38 is…, is present on the surface of most myeloma cells. Is it on the surface of all myeloma cells and is it present on other cells which sometimes can be problematic?

Dr. Torben Plesner – That's a very important set of questions actually. In general, myeloma cells express very high levels of…, of CD38 and that is probably why daratumumab is such a good drug to…, to kill myeloma cells. So, there is a huge difference between the level of expression of CD38 on…, on myeloma cells as…, as compared with other cells in the body. When we started up with the clinical trials for daratumumab, we were very nervous about the possible side effects that could emerge because CD38 molecule is indeed widely expressed on body cells, human body cells, and it was very difficult to make preclinical studies with animals because there is no cross reactivity with…, with the mostly used laboratory animals. So, we had to jump directly, almost directly from the test tube to the…, to the clinical situation of the patients. So, we were very careful when we started with extreme low doses to look for toxicity or side effects and very…, very luckily, we had very, very little signal in terms of side effects. We do see… With the standard dosing of daratumumab, we do see some infusion-related reactions such as nasal congestion and coughing and asthma-like symptoms that seems to be some irritation from the airways which could be due to the fact that the CD38 is expressed by the epithelium of the airways, so…, but this…, these reactions appear with the first infusion and sometimes in a few patients with the second infusion as well, but it can be managed by premedication and…, and after one or two infusions, this subsides and we can continue treatment with daratumumab for months and couple of years have been done now without any side effects at all.

Gary Petersen – Okay. Well, thank you. I believe that the daratumumab makes the myeloma cells more visible to the patient's own immune system and, you know, as the disease progresses, immune systems gets, you know, gets less effective. So, wouldn't it…, if used as early as possible in the disease course when the immune system is the strongest improve the outcomes and the efficacy?

Dr. Torben Plesner – I couldn't agree more. We were alluding to the…, the problems associated with CD38 molecules on…, on our body cells before, but certainly there is a set of neurosuppressive cells in the body that also express CD38 and when we treat with daratumumab, they seem to be eliminated along with the…, with the myeloma cells and this seems to release a break that has been put on the immune system so that T cells, T lymphocytes that are the soldiers of the immune system against cancer, they are increasing in number in a manner that suggests a specificity because they are clonal in their reactivity, meaning that families are emerging that we think are ready to attack the myeloma cells and this…, this aspect of immunotherapy, may be they are important. We'll have to study that in more detail, but it may be very important and it may explain why we see so prolonged and sustained benefit from treating with…, with daratumumab, we see early responses within a month, but then we see that the response to daratumumab during prolonged therapy improves with time and this could be caused by this immunostimulus mechanism

by daratumumab.

Gary Petersen – That sounds like this drug has a great future. What I would like to do now is to go to some of the questions from the other panel members and, Jack Aiello, are you there?

Jack Aiello – I am and its nice to meet you, doctor, over the phone.

Dr. Torben Plesner – Thank you.

Jack Aiello – I have some questions. I know that dara was originally approved as a single agent and wonder if you envision it really being used as a single agent today or instead should patients be trying to use it in conjunction with IMiD and dex or…, or get into a trial that does that?

Dr. Torben Plesner – I think I would encourage any patient to…, to participate in the trial if possible. I don't see except in perhaps in very special situations like prolonged maintenance or perhaps in the setting of high-risk smoldering myeloma. Outside of these areas, I don't see daratumumab as a single-agent drug. I think for treatment of full-blown myeloma, we need combinations, but I do see daratumumab as…, as a part of the backbone therapy for multiple myeloma. So, combinations would be the key to success except for perhaps maintenance and…, and high-risk smoldering myeloma, as I mentioned.

Jack Aiello – Are actually maintenance trials there already looking at dara as a single agent for maintenance?

Dr. Torben Plesner – That is planned and ongoing, yes.

Jack Aiello – Okay and when dara was tested as a single agent, I am wondering were there any prognostic factors that resulted in it being more or less effective or did it work just as well if a patient had various high-risk factors?

Dr. Torben Plesner – Yes. You know, we don't have many details of this…, the usual prognostic factors, but my personal opinion is that using daratumumab is more like hitting the target with a shotgun because you have a…, a…, a drug that can attack the…, the molecules on the surface. You are not…, you are not trying to…., to block a…, a subtle pathway in the cancer cells. You are really hitting from the outside. So, this is a major blow, I think, to the cancer cells so it could very well overcome the usual drug resistance mechanisms and this may explain why we see the response to single agent, also the heavily pre-treated patients that are…, that are resistant and had prior exposure to both proteasome inhibitors and IMiDs.

Jack Aiello – And…, and finally, I once heard that it was not possible to design all versions of monoclonal antibodies. Is that true or could there be an all version of dara?

Dr. Torben Plesner – That's…, that's…, that's true. What…, what is being done now to facilitate the…, the use of daratumumab in…, in…, in general practice is that the subcutaneous versions of…, of…, of daratumumab will be…, will be made available. So, rather than giving it by the IV route…

Jack Aiello – Yeah…

Dr. Torben Plesner – …we'll be able to give it as a subcu infusion.

Jack Aiello – Okay. Thank you very much. I'll…, I'll turn it back over to Gary.

Dr. Torben Plesner – Thank you.

Gary Petersen – Thanks, Jack. Appreciate it. Cynthia Chmielewski, are you online?

Cynthia Chmielewski – Can you hear me?

Gary Petersen – Yes.

Dr. Torben Plesner – Yes.

Cynthia Chmielewski – Okay. Good morning, everybody.

Dr. Torben Plesner – Good morning!

Cynthia Chmielewski – Over here, I guess its not as early over in Denmark and thank you for taking your time to answer our questions. My question has to deal with the first one, about the infusion of Darzalex itself. I hear its a very long first infusion and I was wondering if you could tell us why it…, why its so long, what types of pre-meds are needed with Darzalex, what are some of the possible infusion reactions, I know you talked about few of them that we are seeing and how they could be managed, and I…, I know…, I have heard concerns from local doctors' offices or I saw the 9 to 5 schedule that what happens if they are infusing their patient and its taking 14 hours and they don't have staff there to help with taking that first infusion as an inpatient be something be considered and that's it.

Dr. Torben Plesner – Okay. Thank you very much. I would say that the first infusion is…, is a long one to avoid the infusion-related reactions, more…, more like 7 hours rather than…., than 14 hours.

Cynthia Chmielewski – Okay.

Dr. Torben Plesner – So, I think with…, with good planning and pre-medications and in due time you could…, you could manage within…, within a usual working day and after the first infusion, generally, you can speed up infusions to…, to get it in within 4 to 6 hours. So, I think its…, its not that difficult to see daratumumab in an outpatient setting. That's actually what we are doing, also with the ongoing clinical trials, we give it in an outpatient setting, but you need to plan carefully and start early in the morning and the pre-medications, as you asked for, antihistamines, paracetamol and steroids, pretty much like when we are using rituximab or other monoclonal antibodies, the same…, same strategy. If we do during the infusion see…, if we do see reactions to it which could be like shortness of breath or nasal congestion, we…, we pause the infusion for like an hour, give more pre-medications, and then we resume the infusion after an hour of observation when the symptoms have subsided and usually we can get done within usual working day and…, and this I should underscore that this is the first infusion that is problematic. The second infusion is much easier and after…, from then on, from the third infusions and onwards, its…, its really running smoothly without…, without problems.

Cynthia Chmielewski – Okay. Good! I hear you are saying a lot about breathing problems may be associated with that first infusion. Is there a special need to take in people that have breathing disorders like asthma or COPD prior to the infusion?

Dr. Torben Plesner – Yes. That's a…, that's a risk population where we need to pay special attention, I agree.

Cynthia Chmielewski – Okay. Also, I heard that Darzalex can interfere with blood typing for transfusions and also about monitoring your IgG protein. Can you elaborate about why this….

Dr. Torben Plesner – Sure.

Cynthia Chmielewski – …happens and if there is anything that patients should be doing prior to starting Darzalex?

Dr. Torben Plesner – That's two very important questions. There is very weak expression of CD38 on red

blood cells. So, when you infuse daratumumab, it will bind to the red blood cells without causing any harm. This is a very lucky situation. We were expecting that there could be problems out of this, but actually there is no…, no signal from…, from…, from this binding except that if you want to…, to study the patient's blood type for comparison with a donor in the case you want to give a blood transfusion, the blood bank could have problems in separating their findings. So, the advice to patients is that they have their blood typing done before they start treatment with daratumumab so that…, and have a card on them or have it registered in the computer so the blood banks will know what was the blood type, is there any special needs for…, for concern, and then you can…, you can proceed with blood transfusions without any…, any problems. You just need to take care from the beginning before…, before the first infusion with daratumumab.

Dr. Torben Plesner – The second question was that when you infuse the daratumumab, this is a monoclonal IgG kappa type protein and when you have reached the plateau after some infusions, you will see this in…, in many patients emerge as a very subtle M component of IgG kappa type and if this is the same type as the patient had originally, it can be difficult to claim that the patient is in CR after…, after treatment because you will have this residual M component that actually is daratumumab, but Jansenn has devised a way out of this problem by…, by removing the…, the daratumumab from the patient sample so you can see what is daratumumab and what is residual M component of the patient shown.

Cynthia Chmielewski – Okay. So…, and I guess if you are doing a bone marrow biopsy to tell the difference between the two.

Dr. Torben Plesner – Yes, you know, from the beginning, when the patient is diagnosed, you'll have a clear image…, the clear picture of the patient's M component when it comes to type, is it IgG or IgA, kappa or lambda, and we can follow it during treatment from time to time, take new samples and see. If it disappears, as it should, will it respond to therapy and then when we get down into very low levels of…, of M component, which would be like 0.5 g/L, which is a very low level of M component, you'll see this small peak of daratumumab that could potentially interfere with your interpretation if you don't use the method designed by…, by Jansenn…., developed by Jansenn.

Cynthia Chmielewski – Okay. Good. Thank you. And my final question is, we are all excited about Darzalex and we are wondering what types of trials are now enrolling maybe using Darzalex as the combination therapy or in smoldering myeloma and the newly diagnosed. Can you give us the overview of what types of trials are out there?

Dr. Torben Plesner – We have a very important trial for the frontline therapy of non-transplant candidates with daratumumab being a combination with lenalidomide and dexamethasone, that is, the patients are randomized, so everybody is getting lenalidomide and dexamethasone and half of the patients are getting daratumumab on top of that and I think after the French first trial, lenalidomide and dexamethasone are emerging as backbone of frontline therapy for myeloma…, elderly myeloma patients in…, in Europe and with the results from the randomized trial, I…, I expect combination of daratumumab, lenalidomide, and dexamethasone to be the…, the new…, the new backbone for elderly myeloma patients, that is actually two-thirds of the…, of the myeloma population. When it comes to younger patients that are in Europe at least going for hydrotherapy and also undergoing stem cell transplantation, the good news is that daratumumab does not seem to interfere with stem cell collection, so you can safely use the daratumumab in any combination upfront if all you have are the stem cells. Speaking about, as you asked, the smoldering myeloma, I think you have to define the patient as having high-risk smoldering myeloma because many patients with smoldering myeloma can have that disorder for many, many years without developing into a disease that needs treatment, but there are some signs where you can define a patient as having high-risk smoldering myeloma and those patients, I think, are treated on a trial of daratumumab single agent and in some cases also in combination with lenalidomide and dexamethasone.

Cynthia Chmielewski – Okay. Thank you so much for your very thoughtful answers. Gary, back to you.

Gary Petersen – All right. Well, thanks for that, Cindy. I appreciate it. What I would like to do now is to open

the calls up for people to call in and ask you some questions. So, Priya, could you see that?

Priya Menon – Thank you, Gary.

Gary Petersen – …if you have got some people.

Priya Menon – Listeners, if you have a question for Dr. Plesner, please press 1 on your keypads and we can bring you live on air to ask your question. (Pause) Listener calling in…

Gary Petersen – While we are waiting, I have got a question and that is…

Priya Menon – Yeah.

Gary Petersen – Dr. Plesner, you had said that…, that to treat early would be better than… than to treat later and so, I guess, that's going to come up later in the, you know, in the evaluation, but one of the things that I have always wondered is that about 15% of patients are found in stage 1, about 25% of patients are found in stage 2, and about 60% of patients are found in stage 3. So, it looks like we just do…, and I think that, you know, Dr. Morgan from the University of Arkansas for Medical Sciences brought this up and said its almost…, he called it, you know, a scandal that, you know, we don't find this earlier in the disease progression and I was wondering because Denmark has, you know, care for all, I am sure you have got good records and that kind of stuff. Do you…, do you find it better than we do earlier or do you have the same issues and is there anything that, you know, that can be done that you can see to find it earlier before it progresses because it always is easier to treat, you know, and you have a longer life if found early.

Dr. Torben Plesner – I think you are touching on a very, very important issue. It has been shown that…, shown that in myeloma you have a clonal evolution during the course of the disease where the disease often looks quite benign in the beginning, but all the subclones are there. They are present from the…, from the very beginning and with time, with successive courses of therapy, the more resistance and more malignant subclones will emerge and become dominant and finally kill the patient and I think that is the best argument we have for using the very best drugs we have to kill myeloma cells upfront. When the more malignant, more refractory myeloma clones are small in number and perhaps have not developed resistance mechanisms, so we can…, we can eliminate them by early treatment. So, I think the strategy that has been around in Europe at least for many years, that one should be conservative and treat…, treat with…, with simple drugs in the beginning and…, and keep the more advanced drugs for…, for later use, I think that is a wrong strategy. I think what we have…, the data we have suggests that we should bring the best drugs upfront and do our very best to…, to interfere with this clonal evolution that will eventually kill the patient.

Gary Petersen – Right. So…, and how do we, you know… What…, what needs to be done in order to find it early, you know, when its in the very early stages like smoldering and/or, you know, and high-risk MGUS?

Dr. Torben Plesner – I think we need to create awareness about this among our colleagues. Many of the early signs of myeloma are quite subtle and…, and are symptoms that you often find in the elderly population like low back pain and doctors see hundreds of patients with low back pain and…, and…, and not myeloma and then suddenly one of the patients with low back pain has myeloma. So, its…, its so difficult to be a general practitioner and to be able to make the right test at the right time. Often, myeloma is overlooked for even a few years before it becomes a major problem for the patient and evidence…, everybody that that this is…, this is a very malignant disorder. So, awareness among general practitioners, among patients is key to early intervention and greater success.

Gary Petersen – Well, thank you, doctor, and, Priya, would you like to…

Priya Menon – Yes, Gary. There is… We have a listener, person calling in from (718)983-6757, you are on air. Please ask your question.

Caller 1 – Good day, Dr. Plesner, and CureTalks panel. This is Dana Holmes. Thanks so much for taking my call. Dr. Plesner, I am a smoldering myeloma patient. I actually submitted this question, this round of questions, but I had a moment to call in, so I was grateful I was able to get through. I have high risk to progression features per the risk progression models, both the Spanish and the Mayo Clinic, the…, the…, the risk progression models that I guess everyone really uses at this point. So, I would really welcome your thoughts about the Darzalex trials developed for high-risk smoldering patients. Do you believe Darzalex has the potential to be curative or produce a long-term preventive solution in this patient population?

Dr. Torben Plesner – I think daratumumab would be a very important part of this…, this solution, perhaps the most important part. I am not sure if daratumumab can stand alone. I like a lot the combination of daratumumab with lenalidomide and dexamethasone because they play very well together. Lenalidomide is boosting the immune system. Daratumumab is taking, I think, advantage of that. So, they go very well together. What we have been seeing is that after two years of treatment with the combination of daratumumab, lenalidomide, and dexamethasone, the patients, now I am speaking about patients with…, with…, with relapsed refractory myeloma that are responding to the combination. We see that they become after a while in complete remission, they become more and more worried about the side effects. The side effects of the treatment come from…, from lenalidomide and dexamethasone. So, what I could see was an initial period where the treatment is used with daratumumab in combination with lenalidomide and dexamethasone and after two years or so, one could perhaps could change it with daratumumab as…, as maintenance therapy. What is really going on in the patients, we cannot tell you because what we see is just that the signs of disease have disappeared, the M component is gone, there is no further myeloma cells in the bone marrow, and the patients are doing very well.

Caller 1 – And these are…, this is the refractory and relapsed myeloma group?

Dr. Torben Plesner – This is the group where we have two years and more of experience, yes.

Caller 1 – Wow!

Dr. Torben Plesner – So, for the…, for the…, for the smoldering myeloma, I think the result would be even better, but the…, the balance between…, I am sure the dara should be on all the way also in the maintenance setting, but the…, the…, the duration of the, you could call it a kind of induction therapy with lenalidomide and dexamethasone combination with daratumumab, what I see is that the side effects become more troublesome after a couple years.

Caller 1 – Because of the Rev and the dex, the Revlimid and the dexamethasone?

Dr. Torben Plesner – Because of the…, yes, the Revlimid and dexamethasone, yes.

Caller 1- Uhmm… Do you foresee such a trial being developed for smoldering patients or is it too early because of the…, the…, the monotherapy trials really haven't been completely accrued yet?

Dr. Torben Plesner – I think we will have to do the monotherapy first, but we know from the Spanish study, I am sure you are aware of that, that lenalidomide and dexamethasone make a difference as compared to watch and wait. You can…, you can criticize the study because the smoldering population was not very well defined because they used conventional x-ray to determine if the patients had osteolytic lesions or not and we know that its not sensitive enough because CT scans are needed to provide the best sensitivity. So, probably in the Spanish study, we had patients with…, with…, with myeloma with osteolytic lesions that could have been found by…, by CT scans, but even then I think what we have learned from the Spanish study of Dr. Mateos and her colleagues is that treating myeloma early is a good thing to do before damage has…

Caller 1 – Well, that…, that sounds exciting because from a patient's standpoint, from a smoldering myeloma patient standpoint, the watch and waiting is for the birds to be quite honest with you.

Dr. Torben Plesner – Yeah.

Caller 1 – Dr. Plesner, is there a way to determine who would respond to Darzalex before beginning treatment? Is there a way to test the cells to see if it would actually work?

Dr. Torben Plesner – No. I think…, I think you have to jump…, jump on to treatment, jump into it.

Caller 1 – Uhmm… Okay. And what about…, is this a longstanding antibody or do you…, in other words, once you stop using it, do you lose the actual antibody? It doesn't remain in your body for ever.

Dr. Torben Plesner – No, no. It is within a couple of months.

Caller 1 – A couple of months. Okay. Well, thank you for that insight. I appreciate it.

Dr. Torben Plesner – You will have to stay…., you will have to stay on therapy.

Caller 1 – Uhmm… Which of the three trial arms do you feel would be most beneficial for the smoldering patients? I am…, I am presuming it would be the intense arm which is the long-term arm.

Dr. Torben Plesner – Yes…

Caller 1 – I know they haven't been able to answer the questions and that's why there are three trial arms, but from what I am hearing throughout this discussion, it just makes sense that…, that intense arm is the one to…, to stay on to…, to have the Darzalex consistently in your system, particularly if it…, if it doesn't remain in your body long term.

Dr. Torben Plesner – Yes, I agree that the continuous treatment seems to be the…, the…, the answer. We are…, we are all dreaming about cure of myeloma.

Caller 1 – Yeah.

Dr. Torben Plesner – …and I don't know what… ,what we need to…, to achieve this…, this goal, but definitely the early treatment of high-risk smoldering myeloma would be one area where you could be successful.

Caller 1 – Uhmm… If…, if a smoldering patient were to engage in this particular monotherapy trial and down the road someone developed a trial combining it with Revlimid and dexamethasone, could a patient potentially cross over into such a trial or do you think they would be excluded?

Dr. Torben Plesner – If you want a trial, you cannot jump to another one. You will get excluded, but if the treatment is developed and approved, then you can leave the trial without any problems and then go on an approved type of combination.

Caller 1 – Okay. Dr. Plesner, thank you so much for your insight and for your time today. I very, very much appreciate it.

Dr. Torben Plesner – A great pleasure.

Caller 1 – Thank you, Sir.

Priya Menon – Thank you, Dana. We have a caller. Listener calling in using (602)309-1177, you are on air. Please ask your question.

Caller 2 – Dr. Plesner, my name is Robert Jameson. Thank you for being here this morning.

Dr. Torben Plesner – Sure.

Caller 2 – I…, I have two…, two questions for you. Of course, one of them relates to the diagnosis part of multiple myeloma and then the second one I would like to talk about testing along the way after you are on Darzalex. So, I was 58 years old when I actually initially went to my knee doctor and he did a sed rate test and realized there was something wrong with me. He eventually put me back to my primary care physician who did another sed rate test and determined the same thing. He sent to me a rheumatologist who did a sed rate test and decided I had MGUS, who finally sent me to a hematologist. The hematologist did blood testing on me and determined that I have the M spike and was just going to watch it as smoldering myeloma. Eventually, and this is about a six-month period of time, my calcium level got to 20 and I wound up for hypercalcemia in an emergency room and one thing led to another, where they finally brought in the oncologist and was able to do a bone marrow biopsy and determine that I had indeed multiple myeloma. My question on…, on this first part is if my hematologist sees that I have an M spike and it's high, why isn't he compelled to do a bone marrow biopsy? I…, I feel like I went from stage 1, or actually smoldering myeloma, to stage 3 which is where this was diagnosed while I was being bounced around to specialists and wasted lot of time and could have improved my overall prognosis. Okay. So, that would be question #1.

Caller 2 – Question #2, because I became a…, a myeloma patient, you know, I am being treated at MD Anderson over in Gilbert here which is great care, I am grateful to them. I was put on a couple of different regimens. What worked best for me in the…, in the long run was Revlimid. Eventually, I had a stem cell transplant and unfortunately it failed after about six months. My…, I have a IgA disease and my kappa light chain ratio climbed within about a two-month period. So, they started me on Darzalex. I have had three infusions now and my question on this part of it is, why do I have to wait for eight weeks before they do the first blood test at least to see how my kappa light chain ratio is. So, those are my two questions.

Dr. Torben Plesner – (Laughter) Myeloma can be a very tricky disease to diagnose. When you see a patient with…, with an M component, did you have a complete M component with heavy chain or was it just light chain?

Caller 2 – Light chain.

Dr. Torben Plesner – Light chain only?

Caller 2 – Yes.

Dr. Torben Plesner – Yeah. Umm…. We…, I think in Denmark we would…, we would do a bone marrow examination upfront with a…, with a kappa light chain signal and as part of the workup, we think that it is essential to use the most sensitive technique to reveal bone disease which could be the reason why you developed the hypercalcemia. So, in our hands, a CT scan of the axial skeleton is standard of care. On top of that, we use conventional x-ray for the extremities and the skull.

Caller 2 – Right.

Dr. Torben Plesner – So, this would be with the bone marrow, our primary workup and then we would look for evidence that this situation needs intervention, needs treatment and if you heard me before I think that early treatment is important to have the best results before you have the emergence of more resistant and more malignant clones. So, early treatment is…, is the key to success and why you needed to wait for, you said, eight weeks before you had testing of the kappa-lambda ratio….

Caller 2 – Yes, that's what my schedule shows. I am…, I am being infused for…, every week for eight weeks…

Dr. Torben Plesner – Yeah, yeah. Yeah.

Caller 2 – …and then after…, then after eight weeks, they are going to do a test to see how…, how its working

and that's kind of my question. I am just so not familiar with the drug. Why are we waiting eight weeks? Is it…, does it take that long for you?

Dr. Torben Plesner – We would do…, we would do the testing of the M component or the kappa-lambda light chain ratio on a monthly basis, that is every four weeks.

Caller 2 – Okay. All right.

Dr. Torben Plesner – Just to…, just to make sure that we are on track.

Caller 2 – So, eight weeks, pardon me, four weeks would be early enough to see a change if there was going to be one.

Dr. Torben Plesner – Yeah.

Caller 2 – Then, I guess I do have a third question. What do you think the percentage of efficacy is with all patients now, you know, I…, I was never in…, I was never in a trial, so never really had refractory to anything, so…, and I know this is a little bit of a loaded question, but what is the efficacy going to be for all patients on Darzalex? Like, what would make it stay right out of the gate? Or, is that…

Dr. Torben Plesner – The experience…, the experience we have from trials, that relates to the patients that are heavily pre-exposed to standard therapy like IMiDs, lenalidomide, pomalidomide, so…, so, proteasome inhibitors such as bortezomib and in some cases also carfilzomib and also the majority had been transplanted.

Caller 2 – Right.

Dr. Torben Plesner – So, what we…, what we know…, what we know is that this heavily pre-treated population of patients and that we can achieve a response in about one-third of the patients, but if you are starting earlier on daratumumab, your chance of having a successful outcome is…, is…, is much lessened. I know that the daratumumab is…, is approved in the United States as a single-agent therapy. Can you use it in combinations? Is it…, is it permitted now? Is it…, is it supported…, financially supported by your system? The reason why I am…, the reason why I am asking is that I think that…, that the daratumumab is doing great on its own, but its…, its…, its much better in combination with lenalidomide or perhaps even pomalidomide.

Caller 2 – In my case, what they are doing is, they are doing the Darzalex with dexamethasone.

Dr. Torben Plesner – Yeah. So, you are not refractory to lenalidomide?

Caller 2 – No. No. The only reason they stopped it was unfortunately I had blood clots and those turned into pulmonary embolism. So, they took it off. It actually worked very well…

Dr. Torben Plesner – Yeah.

Caller 2 – …and I was so…, so close to the end of the therapy, they just decided to go ahead and…, and move forward with the stem cell transplant.

Dr. Torben Plesner – Yeah.

Caller 2 – So, no. I…, I worked well with it. It just…, and then of course afterwards we tried to use it as a maintenance but because its so toxic, it was just peaking up my…, my blood numbers and we just couldn't get them back. So, that's…, that's when we decided to switch over to…, to the Darzalex.

Dr. Torben Plesner – I do…, I do have patients that have had complications on the lenalidomide like

pulmonary embolism…

Caller 2 – Yeah.

Dr. Torben Plesner – ..., but I…, I put them both back on therapy after a while with combination of low molecular weight heparin and aspirin. I…, I use both types of anticoagulants to…, to prevent new thrombosis from developing. So, I think it…, it…, it could be done in a…, in the safe manner to…, to resume the dexamethasone therapy if you have daily low molecular weight heparin along with aspirin, so you are inhibiting the coagulation system in two different manners.

Caller 2 – Hey, that's interesting you say that because one of my…, one of my comments to the oncologist was that they put me on lenalidomide, but they did not put me on any anticoagulants, so I was very susceptible to any of the side effects when it comes to that, that it was going to happen, in short.

Dr. Torben Plesner – Yeah.

Caller 2 – So, you know, only after…, afterwards did they finally put me on warfarin to use as an anticoagulant, but it was too late then, right?

Dr. Torben Plesner – Yeah. I am not very fond of warfarin, but…, but I think in your case it could…, it could…, you could safely resume the lenalidomide, dexamethasone if you had this cure, anticoagulation therapy with low molecular weight heparin in…, in combination with aspirin.

Caller 2 – Yeah. Its…, its a bit of work to get the…, get the…, get the anticoagulant rate correct, you know, and finally they have taken me off of that now that I am on the…, now that I am on the dexamethasone or the Darzalex…

Dr. Torben Plesner – Yeah.

Caller 2 – So, I am…, I am glad to be off of that. Anyway, I am very anxious to see in my case, they are going to wait eight weeks, I mean just to see what the results are.

Dr. Torben Plesner – I hope the best for you.

Caller 2 – Thank you very much and I…, I appreciate your comments and…, again thank you for being here.

Priya Menon – Thank you. We have just two more minutes. We could just take one more caller. Person calling in using (720)371-6410, you are on air. Please ask your question.

Caller 3 – Good morning! I am _____[00:58:51]_____ and I appreciate your…, your time and experience. What has been your experience with Darzalex and late-stage plastocytomas?

Dr. Torben Plesner – The question was not easy to hear, but I think its…, the question is, what is the experience with Darzalex and extramedullary plasmacytomas?**C**

Caller 3 – Yes.

Priya Menon – Yes.

Dr. Torben Plesner – My expectation is that they would be sensitive to Darzalex.

Caller 3 – Have you seen this in any…, any…, in any trial to this point?

Dr. Torben Plesner – We do see patients responding, including patients with extramedullary disease, yes,

and we can follow the extramedullary disease manifestations by CT scans, repeated CT scans, and we can see them disappearing, yes.

Caller 3 – Thank you. I appreciate…, I appreciate your efforts and…, and thank you very much.

Priya Menon – Thank you. Its almost…

Dr. Torben Plesner – You are welcome.

Priya Menon – Our hour is up. Dr. Plesner, thank you very much for that informative session. Gary, Jack, and Cindy, thanks for your participation. This talk will be made available on CureTalks' website along with its transcript. We will be continuing our talks on upcoming immunotherapies in myeloma with Dr. Saad Usmani in March. Please visit curetalks.com for details of our upcoming talks. Thank you very much, everyone. Thanks a lot.

Dr. Torben Plesner – Thank you.

Priya Menon – Bye, bye.

Gary Petersen – Thank you, doctor. You did a wonderful job.

Dr. Torben Plesner – Thank you very much. It was a great pleasure to be with you.