Nonsecretory Multiple Myeloma: New Options in Assessment and Treatment

Hallmark of most multiple myeloma cases is the persistent production of some form of immunoglobulins, a phenomenon that brings the disease to attention. However, there is a subset of multiple myeloma patients who do not secrete immunoglobulin or its component parts into either the blood or urine, hence called non-secretory myeloma.

Some non-secretory myeloma patients may produce the immunoglobulin proteins but they have defects in secretion.

Due to lack of these protein biomarkers in blood and urine, it may be difficult to assess and treat the disease. Our myeloma panel is talking to Dr.

Frits Van Rhee about latest developments and new options available in assessment and treatment of nonsecretory myeloma.

Full Transcript:

Priya Menon – Good evening and welcome to CureTalks. This is Priya Menon joining you from India on CureTalks' 121st episode; and today, we are discussing nonsecretory multiple myeloma, new options in assessment and treatment. My co-host for the talk is myeloma advocate and editor of myelomasurvival.com, Gary Petersen. Joining Gary on the panel is myeloma advocate, Jack Aiello. Due to unforeseen circumstances, our panelist, Yelak Biru, is unable to join us today and we regret this.

Priya Menon – The hallmark of most multiple myeloma cases is a persistent production of some form of immunoglobulins, a phenomena that brings the disease to attention; however, there is a subset of multiple myeloma patients who do not secrete these immunoglobulins or its component parts into either the blood or urine, hence called nonsecretory myeloma. Some nonsecretory myeloma patients may produce the immunoglobulin proteins, but they have defects in secretion. Due to lack of these protein biomarkers in blood and urine, it may be difficult to assess and treat the disease. Today, we are talking to Dr. Frits Van Rhee of UAMS about latest developments and new options available in assessment and treatment of nonsecretory

myeloma. Dr. Van Rhee, welcome to Cure Talks. It's a pleasure to have you with us again.

Dr. Frits Van Rhee – Thank you very much for inviting me, and its a pleasure to be here.

Priya Menon – I will be now handing over to Gary who will begin with the discussion; and before that, I would like to inform our listeners that we will be addressing questions sent in via email and posted on the website. So, if you have a question for our panel, please email it to priya@trialx.com or you can also post it on the CureTalks' website. With that, I hand over to Gary to introduce our expert and begin with the discussion. Gary, you are on air.

Gary Petersen – Yes. Thank you, Priya, and thanks to TrialX for bringing us this great forum for myeloma patients. Dr. Van Rhee is a Professor of Medicine in the College of Medicine's Department of Internal Medicine. He is also the Director of Development and Translational Medicine at UAMS Myeloma Institute. He earned his medical degree in Rotterdam, Netherlands, and his Ph.D. at the University of London. He is trained in Internal Medicine and Hematology in the UK and in Bone Marrow Transplantation at John Radcliffe University Hospital in Oxford and Royal Postgraduate Medical School in London. He is a Fellow in the American College of Physicians. At UAMS, he holds the Charles and Clydene Scharlau Chair Hematological Malignancies; and prior to joining UAMS, Dr. Van Rhee was an Associate Professor of Medicine and Director of Cellular Immunotherapy and Transitional Research at the University of South Carolina and a Fellow at the National Heart, Blood, and Lung Institute at the National Institute of Health in Bethesda, Maryland. Van Rhee treats patients with multiple myeloma and related hematologic malignancies. He is also considered an international expert on Castleman's disease and I think that's a…., and he also has many other affiliations as well, but one thing I wanted to say is that his work in both myeloma and in Castleman's have been rewarded and specifically in Castleman's he was awarded the Castleman's Disease Warrior Award for Best Physicians of the Year by the Castleman's Disease Coordinating Network, which is CDCN.

Gary Petersen – So, if you think myeloma is an orphan disease with 30,000 or so newly diagnosed, Castleman's is just 75 to 8,000. So, Dr. Van Rhee goes for the hard things, but one thing I wanted to say is that its not only what he knows, but who he is and presenting the award to Dr. Van Rhee was Dr. Fajgenbaum, MD, MBA, and an Associate Professor of Medicine in the Division of Translational Medicine and Human Genomics at the University of Pennsylvania and Co-author and Executive…., Co-Founder and Executive Director of the Castleman's CDCN, which he says and I think this is important. Dr. Van Rhee has been the leader in the field of Castleman Disease for over a decade. I feel incredibly fortunate to have Dr. Van Rhee as my doctor. As a patient, he saved my life three times; and as a fellow medical professional, I can say with a 100% certainty that I have never met or interacted with another physician that is anything like Dr. Van Rhee. He is the ultimate care provider and the ultimate doctor. So, when you have that kind of glowing referral from the head of the CDC and also who trusts his care to Dr. Van Rhee, I think it says a lot. So, thank you, Dr. Van Rhee for coming with us today, and I hope I didn't embarrass you with that embellishment.

Dr. Frits Van Rhee – Thank you very much for your kind…, for your kind words, and I am very grateful for all your very generous compliments.

Gary Petersen – Thank you! Doctor, first off, you know, I am not sure everybody really understands what nonsecretory myeloma is and if you could please explain what nonsecretory myeloma is and why it is different from majority of myeloma, for the audience.

Dr. Frits Van Rhee – Myeloma, as Priya already so eloquently pointed out, it is a cancer of plasma cells and the job under normal circumstances of plasma cells is to make antibodies and when they become cancerous, they start to make one specific antibody which we refer to as the M spike myeloma protein and this antibody can be measured in the peripheral blood and also in the urine and it can be used as a surrogate for response. Its a very convenient way of monitoring and detecting the disease. Now, about 1% to 2% of patients do not produce the myeloma protein or at least its not present in their peripheral blood. So, the criteria for diagnosing nonsecretory multiple myeloma is that you should not have myeloma protein

detectable in the peripheral blood. Also, some patients make part of the myeloma protein, which is called the light chain. An antibody molecule consists of a heavy chain and then a light chain. So, there is now also a serum free light chain assay and that assay needs to be negative as well. So, you should not produce both the M protein and the light chain in the peripheral blood and lastly, a 24-hour urine should be negative. In other words, you should not detect any abnormal protein by protein electrophoresis in the urine sample. So, in essence, you lose one marker of your disease and that is the myeloma protein. As such, there are two reasons why patients don't have myeloma protein or light chains in the peripheral blood. The first reason, which is quite rare, is that the myeloma cells are not producing it. The second reason and that's much more common is that the myeloma cells are actually still producing these proteins, but they are not excreting it into the peripheral blood. So, that's the most common kind of so-called nonsecretory multiple myeloma.

Gary Petersen – Okay. Now, if you don't have these markers, you know, we would…., you know, they would say you have high urine, that's why we are going to check further and you have, you know, high protein in your urine and you've got protein in your serum, in your blood and that's how we find, you know, this. So, how can we find it before it, you know, if you can't see it kind of the normal way, how do you find it before its out of control or in stage 3? How does it present itself so people know that they have myeloma or they know people who get…, nonsecretory myeloma usually end up, you know, at the end of the rope?

Dr. Frits Van Rhee – Well, it is true that you would lose an important marker to detect the disease. So, in some patients diagnosis can be delayed. Obviously, myeloma can cause anemia. It can cause problems with the bones, sometimes fractures in the spine or in the lung bones. It can cause high calcium and sometimes also abnormal renal function, kidney function and these findings can prompt searching for the myeloma protein, which obviously will be negative in this group of patients, but then a bone marrow biopsy or a biopsy of an abnormal area in the skeleton can lead to the diagnosis. During the staging and looking at the ISS, the International Staging Criteria, actually stage 3 is less frequently present in nonsecretory myeloma. The main reason for that is that these patients are not producing the myeloma protein and it can therefore, not affect the kidney. So, there is no kidney impairment; and if you have abnormal renal function, then one of the other markers for myeloma, which is called B2M or beta-2 microglobulin is not elevated and that's an important marker used in the staging system to define stage 3. These patients have a high beta-2 microglobulin; and obviously, there are some advantages to not having the myeloma protein circulating as well since these patients don't develop organ damage due to deposition of light chains in the kidney or in the heart as amyloid or light chain deposition disease. Furthermore, the whole myeloma protein in some patients can be very high and make the blood sticky or viscous, something we call as hyper viscosity syndrome and that is something, which also does not occur in patients with nonsecretory myeloma. So, there are some advantages to not having this protein circulating, but it certainly…, it certainly can delay diagnosis. You are losing important marker for monitoring the disease.

Gary Petersen – I know that we had one of our panel members, Pat Killingsworth, I am sure you've heard of Pat and Pat was a nonsecretor and he…., we unfortunately lost him not that…, but little over a year ago and, you know, that was one of his problems. He couldn't…, you know, he had no M spike, he had no light chains that were out of rack. He had very low plasma cells in his bone marrow, but he did… Even at 0.4, he would have terrible bone pain and bone destruction. So, I was wondering, do you find that nonsecretors tend to be found because of bone destruction?

Dr. Frits Van Rhee – Yeah, I think that is a more common presentation in nonsecretory myeloma, that the disease is found as a result of problems with the bones and other possible presentation obviously as a result of that is high calcium which can make patients confused and obviously as the bone marrow is more heavily infiltrated, anemia can occur.

Gary Petersen – Okay. So, you can have anemia as well. All right. So, there are some advantages to nonsecretory myeloma and that is that, you know, you don't have all these nasty light chains and proteins going through your body, messing you up, but on the other hand, its tougher to find. So, given this, I guess that will answer my next point but maybe not, maybe you've got another read on that, is given the fact that what…., you know, given the fact that its hard to find and why is the life expectancy of nonsecretory myeloma

patients half again longer than that for the average myeloma patient and I mean by that, is I guess Mayo Clinic had done a retrospective analysis of patients between, I think it was, 2001 and 2012 and found that there is, like I think it was 8.3 year life expectancy for the nonsecretors and 5.4 for the secretors.

Dr. Frits Van Rhee – So, I think one of the important things to realize when you survey the literature that I would agree that the outcome of patients for nonsecretory myeloma certainly doesn't appear to be worse; however, these patients are typically not enrolled on clinical trials because all clinical trials usually stipulate that you need to have a myeloma protein detectable in order to monitor the response. So, you are talking about doing analysis retrospectively of patients not treated on a clinical trial. Then, the other point to make is that a lot of the published studies include patients who were treated before the free light chain assay became available, and about 60% to 70% of patients who appear nonsecretory will have secretion of free light chains when the free light chain assay is used. So, some of the patients in these studies, when you look at them, they may actually not really have nonsecretory multiple myeloma and lastly, because nonsecretory myeloma is such a small percent, in order of 1% to 2% of myeloma patients have diagnosis, we are dealing with very small numbers of patients. The study that you quoted I think had 36 patients in it after 2001. So, we have data on small numbers of patients and there are limitations to the data sets; however, it does not appear that these patients do worse when they have nonsecretory multiple myeloma diagnosis.

Gary Petersen – Okay. Well, thank you so much. So, the next question is really what all the listeners are here waiting to hear and that is, what are the latest developments and new options available in assessing and the treatment of nonsecretory myeloma?

Dr. Frits Van Rhee – If you think about myeloma as a disease in which you can monitor certain things, the things that one usually looks at is, one, the myeloma protein and the light chains and the urine and that as such you will lose and you are left with looking at the bone marrow and doing imaging studies to look at bone disease and these become more important in this patient group. So, there is more reliance on doing, one, bone marrow examination and, two, imaging and it has become increasingly clear that the skeletal survey which to some extent for very long time has been the standard of care for assessment of multiple myeloma patients perhaps should be replaced doing MRI or PET scan studies in these patients for monitoring the disease. When you compare the MRI and a PET scan, the MRI is very good at diagnosis to give you anatomic information. They can see the bone marrow lesions very well on MRI scanning; however, the changes in MRI with prolonged treatment are relatively slow. PET scan is based on the uptake of sugar-like dye into the myeloma cells which are alive and the changes in the PET scan are much more dynamic, much more quickly after treatment. So, the changes in the PET scan occur much quicker. So, this patient will particularly benefit from monitoring a PET scan. In terms of treatment, there is as such no evidence to suggest that these patients fare any worse or significantly better than other patients. So, they don't really need any different treatment approach. I think the main difference lies that in the monitoring of the response to treatment rather than applying different therapy.

Gary Petersen – So, do you do gene expression profiling on or is there just not enough secreted in the bone marrow to evaluate?

Dr. Frits Van Rhee – The gene expression profiling and sequencing studies do not involve the myeloma protein as such. Usually what is being done is that a bone marrow is being sampled, the myeloma cells are purified, then the genetic material is extracted and further examined. One test that we do is the gene expression profiling, and there are obviously now more sophisticated analyses can be done as well, but you don't need the myeloma protein as such for that, rather the myeloma cells and the answer is yes, we do gene expression profiling on myeloma and the patient's gene expression profile, which gives you a molecular picture of the myeloma, is an important prognostic tool. About 85% of patients at diagnosis have low-risk myeloma. In our program, low-risk myeloma doesn't mean little treatment. It means if you are fit and well, a very good outcome with a significant amount of treatment. High-risk myeloma which 15% of newly diagnosed patients have is characterized by a higher relapse rate. We have a different treatment protocol for these patients.

Gary Petersen – Okay. What is that treatment protocol? I know that you guys are looking in it for a long time and really nobody has made much of a breakthrough, I don't believe in high-risk.

Dr. Frits Van Rhee – Well, I think the first point to make is that in the myeloma community at the moment, there is no consensus how to…,, how to define high-risk myeloma. There are different ways to looking at the myeloma cells at the genetic level. I think we use a very stringent, a very strict definition of high-risk myeloma. So, in our hands, fewer patients are high risk perhaps than at other centers and at the moment, we are incorporating carfilzomib at all phases of the treatment, that is during induction when the bone marrow, during the stem cell transplantation phase, the consolidation, and the maintenance after the transplants, we try to give our treatments quite close together. We also combine different drugs in order to try and let the drugs work together rather than give necessarily very high doses of drugs and we have also started to introduce the new antibody, particularly the Darzalex or the daratumumab antibody.

Gary Petersen – And that's in consolidation and induction, consolidation and maintenance, or where does it go?

Dr. Frits Van Rhee – We find that in the high-risk patients, as I said, they are characterized by increase of relapse which particularly occurs during consolidation and maintenance and that's where we want to add, that's where we are adding the daratumumab treatment, the Darzalex treatment, the antibody treatment.

Gary Petersen – Oh, okay. So…., so, it sounds like there is really, you know, you look at gene expression profiling, determining if there is any…, anything in that that might require a different method of attack, but in general, you've got a pretty good, you believe, idea on how to go after the low-risk population and are working on something else for the high risk. At this point, I would like to go on to Jack Aiello and Jack is going to ask his questions. He is going to then ask Yelak's questions and he promised to try to copy his accent, which I know, this is going to be funny, which is Yemeni, I think, and then he'll ask the questions from the callers as well. I've got a little cold, so I am a little under the weather, but Jack will take over for me. Jack, you there?

Jack Aiello – I am here.

Gary Petersen – Okay.

Jack Aiello – Dr. Van Rhee, I asked my Dutch wife, is your last name pronounced Rhee or Rhee?

Dr. Frits Van Rhee – Well…

Jack Aiello – She wasn't sure.

Dr. Frits Van Rhee – You have to say Rhee.

Jack Aiello – Yeah, that's what she thought too. Okay. So, I'll call you Dr. Van Rhee, if that's okay.

Dr. Frits Van Rhee – Thank you very much.

Jack Aiello – So, I'd always heard that there are some myeloma patients that start off as secretors and can become nonsecretors. I actually think that's what happened with Pat Killingsworth and so I wonder if you can confirm that's true and can it also be vice versa? Can you start off as a nonsecretor and become a secretor?

Dr. Frits Van Rhee – I think it is very important to recognize the difference between nonsecretory multiple myeloma at diagnosis and at relapse. At diagnosis, the patient seems to have similar outcome with treatments compared to patients who have secretory myeloma, in which there is a myeloma protein largely undetectable. At relapse, what can occur is that the patients lose the production of the whole myeloma

protein and only start making light chain. This is referred to as light chain escape and others can stop producing any myeloma protein altogether or only produce very little of it and this usually means that the disease has changed its nature and is becoming more persistent and in some cases also more aggressive. This likely occurs because of additional genetic alterations, genetic mutations in the plasma cells, which interfere with the production or the secretion of the myeloma proteins.

Jack Aiello – So, the patients then who think they…, first of all they were secretors and think they have achieved a great response from the treatment could actually be mislead in thinking those results were good if they become nonsecretors.

Dr. Frits Van Rhee – That is correct and we tend to follow our patients not only by doing myeloma protein assays, which are obviously very important, but we also do at regular intervals a bone marrow examination and imaging studies. So, those are the three main modalities that we use to monitor for disease recurrence.

Jack Aiello – Yeah. I am sorry, go ahead.

Dr. Frits Van Rhee – And obviously in cases where patients either have nonsecretory myeloma at the onset or where it occurs at relapse, the bone marrow examination and the imaging studies become more important.

Jack Aiello – Yeah. I'd always heard that patients should get another bone marrow biopsy when they do relapse, but you are saying its actually more important to get them kind of on a regular basis even if they are in a good response just to make sure there are no surprises.

Dr. Frits Van Rhee – That's right. Obviously, bone marrow examinations are unpleasant and one can't do a bone marrow exam at the drop of a hat, but, in general terms, when patients are longer out, we will do at least yearly bone marrow examination to confirm that there are no myeloma cells detectable, even when the myeloma protein is negative and that's even more important if the patients are nonsecretory.

Jack Aiello – Yeah. Okay. Thank you! I was going to ask you about gene expression profiling, but I think I heard the answers to Gary's questions are that there are really no differences in gene expression profiling between secreting patients and nonsecretors. Each patient is different and there is no…, you can't say that well, if you are a nonsecretor, you are more likely to have a more positive gene expression profiling. Is that correct?

Dr. Frits Van Rhee – So, the gene expression profile will tell you more than the risk that the myeloma has of behaving in a bad way. So, there is no reason to assume that patients with nonsecretory myeloma have a worse gene expression profile; however, it is possible that they belong to different subtypes of myeloma defined by gene expression profiling or other names and nobody really has looked about in any systematic fashion. Those of the listeners who are little bit more in tune with the genetics, there is some inkling perhaps with patients with translocation 11;14, are more likely to have nonsecretory multiple myeloma, but this has never been confirmed or looked at systematically.

Jack Aiello – Interesting! I have a question with respect to MRD or minimal residual disease. Is it correct that there is no reason a nonsecretory patient shouldn't be able to have MRD testing via flow or sequencing using bone marrow biopsies?

Dr. Frits Van Rhee – I think the MRD testing is increasingly used and obviously we do MRD testing using flow cytometry on all the bone marrows that we cure. The flow cytometry test has some advantage over just doing the biopsy. The biopsies can sometimes be a little punchy. In other words, in some areas, there is more myeloma than in others and this flow cytometry test is used as an useful addition. We know that attaining or becoming MRD negative in the bone marrow is important and most studies being MRD negative are associated with a better outcome. In our data sets, we find that there is one particular subtype of myeloma where MRD…, where becoming MRD negative is probably not that important. Certainly, in high-risk

myeloma, being MRD negative early on in the treatment program is very important in terms of outcome, but we have not proven or that has not been proven in the myeloma field as yet is that altering treatment based on MRD test will improve your outcome, although one would intuitively assume that this would be the case, this actually will be studied in future clinical trials and is as yet unproven.

Jack Aiello – So…, but to summarize, MRD testing via a bone marrow biopsy should be just as accepted for nonsecretory patients as well as secretory?

Dr. Frits Van Rhee – That's correct.

Jack Aiello – Okay.

Dr. Frits Van Rhee – I think it should have the same implication and relevance.

Jack Aiello – And I know they are studying MRD testing via serum. They don't have yet as high a degree of accuracy, but I presume MRD via serum testing would not be effective at all for nonsecretors.

Dr. Frits Van Rhee – No, I don't think that would be the case. The MRD testing in the serum really looks at the DNA, at the genetic material and there are some advantages to doing that on the serum because you would sample the whole body so to speak, not just one site in the bone marrow because one could imagine that these tests could have picked up genetic material coming from a bone lesion in the spine, another bone lesion in the thigh bone, etc. So, in principle, one could get a broader picture with this type of testing and the correlation with flow cytometry testing in the bone marrow is still very early…, very early on and we don't quite know how this correlates with standard response or MRD testing in the bone marrow. So, I think those are very interesting future things to be developed.

Jack Aiello – You mentioned earlier that because nonsecretors don't show an M spike, for example, that they are usually not part of clinical trials and they are not…, they don't quality from an eligibility criteria. If I were a nonsecretor, I would kind of pivoted this and would do whatever is possible to get into trials. Are there more trials that might be open to them if the trials set an eligibility criteria using…, somehow looking at MRD versus M spike improvements?

Dr. Frits Van Rhee – Yes and obviously efforts are being made to use MRD testing as a surrogate…

Jack Aiello – Right.

Dr. Frits Van Rhee – …or outcome and one would hope that the regulatory authorities can embrace this; however, one should also realize that examination of the bone marrow normally does not suffice. I think there is increasing evidence that imaging in multiple myeloma is important and if we are talking about nonsecretory myeloma, we are not only talking about doing bone marrows but probably also following by an imaging modality such as CT/PET scanning and obviously when a company develops a large scale trial that would add very considerably to the cost.

Jack Aiello – Yes. Yeah. Okay. Let me ask a couple of questions that Yelak Biru posed. He asks, even when nonsecretory, can myeloma patients still experience common myeloma symptoms such as bone lesions, renal failures, and can they still be typed as IgG or IgA and whatever kappa and lambda light chains and I am thinking the answers are probably yes and no to those two questions, but can you clarify?

Dr. Frits Van Rhee – So, there are two reasons why a patient doesn't secrete the myeloma protein into the blood or the urine. One is, its not produced only by the myeloma cells, we call that the non-producing myeloma and that's a very rare entity. The more common thing is that the myeloma proteins are still being made in the cell, in the myeloma cell, but they are not being churned out into the blood streams. So, you can actually find myeloma cells and look for the light chains and look for the IgG or IgA. So, its possible to characterize in that way, although that is not routinely done, but its in principle certainly feasible.

Jack Aiello – And the nonsecretory patient can still have bone lesions and renal failures and things like that?

Dr. Frits Van Rhee – Renal failure is obviously less common because these abnormal proteins are not circulating and cannot damage the kidney. So, renal failure is less frequent, but they can certainly have bone lesions and that is very well described in the literature that is, in fact, quite frequent in nonsecretory myeloma.

Jack Aiello – Okay and I think Yelak asks a really interesting question here. He says if imaging tests such as PET/CTs are the ones that are more effective to monitor nonsecretory myeloma, are you aware of any special considerations by insurance companies or Medicare to pay for more PET and CT or imaging studies if a patient is nonsecretory?

Dr. Frits Van Rhee – No, I am also not. The only thing one can do is try to convince the insurance company that its important in this particular patient since one of the other important markers to trace the disease, that is the myeloma protein, is not near. I think in our experience, in general terms, getting CT/PETs and MRI covered is not always easy, but despite the increasing awareness and increasing evidence in the field that these studies are important. So, the answer probably lies in good clinical study and good clinical evidence to show that these tests are important for monitoring and diagnosing the disease.

Jack Aiello – Thank you. Priya, I'll ask a couple of questions that I see as well. Gary asked me to ask those. So…

Priya Menon – Yeah.

Jack Aiello – One question that came in and he doesn't specify if the question is for nonsecretory or secretory patients, but he says I am in remission and have regular blood tests. Again, he doesn't specify what kind of blood tests. He says, are they relevant or are only portions relevant? Have they been a waste of time and money?

Dr. Frits Van Rhee – They certainly have not been a waste of time and money. The majority of patients will have a myeloma protein detectable at diagnosis, either whole M protein or the light chains, and they also very frequently on reappearance of myeloma proteins when they relapse and monitoring of blood and urine is very important to detect relapse. So, I do not think that these tests have been a waste of time and I would encourage the patient to continue to have these tests performed.

Jack Aiello – And if the patient were a nonsecretory patient?

Dr. Frits Van Rhee – If the patient is a nonsecretory patient, then there is obviously not much point in measuring the myeloma proteins. If the patient is nonsecretory and then becoming secretory, in other words, first you cannot find any myeloma protein and the patient relapses and produces myeloma proteins in some extremely rare scenario, which I think we've seen only twice at our center. So, for practical purposes, doing the myeloma markers in blood and urine is not necessary, but obviously, you would want to monitor the blood counts, the kidney tests, and the calcium. So, the other regular blood tests are of importance.

Jack Aiello – Yes. Another person asks, what's your opinion regarding the use of total body MRI for continued followup of nonsecretory myeloma versus the use of PET/CT scans for a patient who is….

Dr. Frits Van Rhee – Well, so, regular MRI looks at distinct body parts, like the spine, one can ask for the arms, the legs, the wrist bone. The whole body MRI uses different principles based on water movements and we look at the whole body and it also gives you some idea about activity of the myeloma. So, it more resembles the PET scanning and, in fact, in some patients for different reasons, the PET scan can be negative and on the whole body MRI, we can still find the disease. So, what is called the whole body MRI is presently being developed at our center and other centers. We have been doing this here for several years

now and I think it needs to be respectively compared to PET scanning and regular MRI to define its true value. Having said that, in clinical practice here, we use whole body MRIs very frequently and they are very, very good at finding relapse early. So, they…, yes, they are useful for patients with nonsecretory disease and could be used instead of a PET scan if an insurance company is not keen on doing PET scans.

Jack Aiello – And one last question, Dr. Rhee…, Van Rhee, came in while we were talking and this person asks, is there a particular combination of therapies that seem to work best in nonsecretory myeloma patients?

Dr. Frits Van Rhee – I think the same treatment that one used for, so called, secretory myeloma for those given to patients with nonsecretory multiple myeloma, so I don't think that they need to have a different treatment strategy.

Jack Aiello – Yeah. Dr. Van Rhee, those are all the questions I have. Priya, I don't know if there is anyone on the phone, the ones that ask questions live, but I assume we appreciate all your answers, Dr. Van Rhee.

Priya Menon – Thank you, Jack.

Gary Petersen – Yeah and it has to do with, you know, because its such a small number of patients, it seems like not many people would have experience with nonsecretors. Do you think its important to go to, you know, a large academic center that might see a few of those versus one that's not quite as, you know, is large and has seen lot of patients?

Dr. Frits Van Rhee – I think that probably applies to a lot of different diseases, particularly when it comes to interpreting what one might do with an MRD test or a PET scan. It is also important to realize that there is really a spectrum between secreting myeloma protein and nonsecreting…, and not secreting the myeloma protein. There are also patients called…, the technical term is oligosecretory or hyposecretory, so they excrete a little myeloma protein and this is particularly an important concept when the patient has experienced relapse or progressive relapse as because what one can find in that scenario is that although there is some myeloma protein detectable, its no longer reflective. It doesn't give you real information about the amount of myeloma in the body, that is the tumor burden, and even in such a patient, we do an MRI or a PET scan, one could see a large amount of disease and a relatively small amount of myeloma protein and the myeloma protein then uses informative value and again this becoming less secretory, although there is still some protein detectable, particularly occurs in patients who are experiencing repeated relapses and there are other modalities such as repeat bone marrow examination and imaging become increasingly important to monitor the disease and the response to treatment. We have looked at all disease that we can see on PET scan and sample different areas are looked at genetic material and the genetic makeup in different areas of the body of the myeloma can be quite different and what one can see in some patients, that if we give a certain treatment, that some areas of the PET scan get better and others do not respond. So, in those cases, the imaging becomes very important. In summary, I think there is value, particularly when the disease is nonsecretory to go to a larger center that is more experienced in monitoring patients with no myeloma protein detectable.

Gary Petersen – Okay. Thank you so much, doctor. Priya, do you have any questions on line?

Priya Menon – No, Gary, and thank you so much, Dr. Van Rhee. Its been a very informative discussion. We have quite people listening to us. If you have a question that you would like to ask Dr. Van Rhee and/or the panel, please press 1 on your keypads and we can bring you on line, on air, to ask your question. I don't think we have anymore questions. So, Dr. Van Rhee, thank you so much for your time and, Jack and Gary, thank you very much for your participation and your questions too, and Gary, hope you get better soon.

Gary Petersen – Thanks.

Priya Menon – This talk will be available on CureTalks' website and we are back again on Friday with the

talk on breast cancer and fertilized medicine at 5 p.m. EDT. So, please visit curetalks.com for upcoming talks. Thank you, everyone! Have a nice evening.

Dr. Frits Van Rhee – Thank you.

Gary Petersen – Thank you.

Jack Aiello – Thank you.