Slide 1: Myeloma–Diagnosis and Treatment Update

OPERATOR:
Hello everyone and welcome to Myeloma–Diagnosis and Treatment Update, a free telephone/web education program. It is my pleasure to introduce your moderator, Lauren Berger, of The Leukemia & Lymphoma Society.

Slide 2: Welcome and Introduction

LAUREN BERGER:
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. And special thanks to Dr. Niesvizky for sharing his time and expertise with us today.

We have over 1,400 individuals participating from across the United States and international participants from Barbados, Bolivia, Canada, Guatemala, Ireland, Jamaica and the United Kingdom.

We’d like to acknowledge and thank Celgene, Millennium: The Takeda Oncology Company, and Onyx Pharmaceuticals, Inc. for their grants to bring you this program.

Before I turn the program over to Dr. Niesvizky, I would like to introduce The Leukemia & Lymphoma Society’s President and CEO, John Walter, who will share a few words. John?

JOHN WALTER:
Thank you, Lauren. I’d like to add my welcome to all the patients, caregivers and healthcare professionals on the program today. We are all fortunate to have as our presenter Dr. Ruben Niesvizky, one of the nation’s leading experts in myeloma. We appreciate his dedication to supporting the mission of The Leukemia & Lymphoma Society through his research and his care of patients living with myeloma. I would like to thank him for taking the time out of his busy schedule to provide us with an update on myeloma diagnosis and treatment.

The Leukemia & Lymphoma Society is committed to bringing you the most up-to-date information about your blood cancer. We know it is important for you to stay current, so that you can work with your healthcare team to determine the best options for the best outcomes. Our vision is that one day the great majority of people who have been diagnosed with a blood cancer will be cured or will manage their illness with good quality of life.

Since 1954 LLS has awarded more than $875 million to fund research, specifically targeting blood cancers. We will continue to invest in research for cures and programs and services that improve the quality of life for patients and families.

This program is one step on the road of your journey to managing your life with myeloma.

Thank you, and I’ll turn the program back over to Lauren.

LAUREN BERGER:
Thank you, John.
LAUREN BERGER:
At this time I am so privileged to introduce Dr. Ruben Niesvizky, Director, Multiple Myeloma Center and Associate Attending Physician, Division of Hematology/Oncology, at Weill Medical College of Cornell University in New York. Dr. Niesvizky, please go ahead.

Slide 3: Treatment for Multiple Myeloma
DR. RUBEN NIESVIZKY:
Hello, everybody. It’s really a pleasure and a privilege to be here and be able to discuss some aspects of the treatment and the diagnosis of multiple myeloma. I have entitled the talk Treatments for Multiple Myeloma: Goals, New Trends and the Future. And I invite you all to visit our website, myelomacenter.org.

Slide 4: Patient/Doctor Experience
And let me start first also to talk about one of my patients, who wrote this book with one of my partners here at The Myeloma Center. And I encourage you to read it. It’s a great book that explains to you step by step everything you want to know about multiple myeloma. It takes you through the journey of a patient, but also tells you about the specifics of the disease.

And since most of the people are interested in knowing about new treatments for multiple myeloma, let me first talk about these new treatments for multiple myeloma.

Slide 5: New Treatment for Myeloma
It was described by Alwall and collaborators, in which they describe a patient with multiple myeloma who had reduction on the globulin concentration from 5.9 to 2.2, and had increase in the hemoglobin and disappearance of the protein in the urine and reduction of the bone marrow plasma cells from 33% to zero. The only thing, that it is really not new treatment for multiple myeloma. As you see in the slide, this was done in 1945 and it was called urethane. I bet that anybody with this type of information will be willing to receive this treatment. And it wasn’t from 1945 to 1960 that it was first tested scientifically.

Slide 6: First Randomized Trial: 1962
And as you can see, Dr. Holland and coworkers did a controlled clinical trial of this molecule, urethane, and randomized 83 patients to be treated either with this agent or with Coca-Cola flavored syrup. Guess who lived longer and who had better outcome? Indeed, it was Coca-Cola.

Slide 7: Photo
Which takes us to the point that everything we do in clinical medicine has to be based with clinical trials demonstration. And that’s a hard pill to swallow when you hear the benefits of natural medicine and alternative medicine without a solid proof of scientific testing. For that we have clinical trials that have allowed us to progress on the field and no longer we use urethane and we base a lot of that on a new era in multiple myeloma as we try to base animal models, scientific community, basic research and clinicians to advance the field.
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Slide 8: Available Options
As you can see in this slide, this has been a slow but steady progress. From 1950 to 1960 treatment was really limited to palliation. Otherwise we only had to treat patients to improve their pain and suffering, but the survival was really not impacted.

It wasn’t until the early 80s in which novel therapy was introduced with the use of stem cell transplant, which improved a step forward in the field.

But it wasn’t until the end of the 90s and the beginning of the 21st century in which we are starting to see in the field advances in stem cell therapy, thalidomide and now bisphosphonates, bortezomib and lenalidomide, which brings us to possible cure.

Slide 9: Myeloma
And also another concept that we have to understand is that multiple myeloma is not one disease, it’s multiple diseases, and it may present with malignant features in some cases and it may present with a very indolent benign fashion. As we move on the field we have learned now with molecular techniques and with cytogenetics, to try to identify those patients who are actually in a worse situation than others. And learn more about their natural history of their disease.

Slide 10: Multiple Myeloma Natural History
For instance, in this slide you can see that at the beginning it’s usually for more than 90% of the patients an indolent state. Either we call it MGUS, monoclonal gammopathy of undetermined significance, or smoldering myeloma. And most of these patients actually require no therapy, but eventually they become with active disease. And we’ll talk more about what active disease is.

But it is considered now that almost every patient has had a prodrome or a preceding indolent condition that will eventually become multiple myeloma. At this point we don’t yet understand which of these patients will require therapy or which of these patients will benefit of any treatment. But as the patient becomes active, therapy can induce responses, and these responses can be variable and patient enjoys good quality of life while they are in this phase or plateau of remission.

Moving through the slide towards the right, you can see that eventually, though, the patient’s myeloma will return in a condition called relapse. And again those relapses can be treated again with further therapy or exchanging therapy A through therapy B, etc., to achieve another quiescent state which is another plateau and remission. And this can be happening several times until, unfortunately, the disease becomes refractory to therapy and the disease and the symptoms progress with the untimely death of the patient.

So it is at this point in which we start intervening with newer therapies to try to resolve the disease at the later stages. And as we see that as patients respond to the new agents, then we can move the agents earlier in the disease to achieve a better control.

Two schools of thoughts, though, is that if we can eliminate those cancer cells that will progress into multiple myeloma in earlier stage we will eventually result in longer response.
Slide 11: Multiple Myeloma
I take you to the next slide, which is a slide from a patient with multiple myeloma. And it has several features. As you see, all these cells with their nucleus have different shapes. Usually the nucleus is towards the side of the cell, or you call it eccentric. And you see in the top left smaller looking normal plasma cells. The plasma cells who are involved in the production of antibodies and these are the myeloma cells. The myeloma cells is the counterpart of the normal plasma cell. But in the middle you see a much larger cell, also with a nucleus towards the side, but in a much larger uglier fashion. And more to the top you see a multi-nucleated cell with many nuclei, identifying another form of cell.

Which also brings me to the point that the cell, the myeloma, is a heterogeneous disease. There is not only variability among different patients, but there’s also variability among each patient. And a condition that now is being talked about very often in our circles, which is what we call clonal evolution. Many start as normal appearing cells, but eventually it evolves in more ugly looking cells, and it’s the therapy that may reduce this transformation or even sometimes enhance it.

Slide 12: Clinical Features
How do we know when those patients who have that indolent MGUS or smoldering progress into what we call active myeloma? Or in other words, who are those patients who require treatment are those who are called active myeloma. And active myeloma is manifested usually by hypercalcemia, which means calcium elevation in the blood, renal disease, which is manifested usually by an abnormal creatinine level in the blood, or nitrogen urea elevation in the blood, which means only that the products of cellular catabolism cannot be dealt properly by the kidney and the kidney cannot eliminate them and that’s why those creatinine and urea nitrogen are elevated in the blood.

And of course, alterations in the bone marrow, what we call anemia, being one of them, but also we could see lower white count and lower platelets as manifestation of the disease.

And perhaps the most dramatic of them is the bone disease or skeletal disorders, which presents with usually with severe pain.

Slide 13: Myeloma End Organ Dysfunction: CRAB
So we use the term CRAB to remember these four aspects of what we call myeloma end-organ dysfunction. C for calcium, A for anemia, B for bone disease and R for renal disease.

Slide 14: Bone Disease
It’s, of course, bone disease, the one that causes the worst symptomatology of the disease.

Slide 15: Bone Disease (con’t)
Almost 80% of the patients eventually will have some sort of bone damage and pain and that is one of our major challenges in treating the disease, how to prevent bone disease and how to treat it when it’s already ensued.

In fact, more than 60% of the patients have some form of bone damage with lytic lesions, what we call lytic lesions, is spaces without calcification or little holes. Demineralization with osteoporosis. And there’s a subgroup of patients that do not have active bone disease.
Slide 16: Photo
Certainly with newer techniques we are able to detect bone disease more often. In this patient of mine, you can see in the top left above the brain, a small collection of plasma cells occurring from the skullcap that is pressing into the brain cavity. And as such, using this technique such as magnetic resonance and PET-CTs, we are able to detect easier, earlier and more accurately the involvement of bone disease, even before it presents bone damage and pain.

Slide 17: Pathogenesis of MM Bone Disease
And it’s because these plasma cells, these myeloma cells as you see in the top of the slide, produce factors that disregulate the bone metabolism. In the bottom of the slide you can see a normal bone or a cartoon of the normal bone with two different type of cells. In the left are the bone-forming cells, which are called osteoblasts, which their normal job is to produce the mineral and the protein part of the bone. Whereas in the right side, you see those purple looking multi-nucleated cells chewing up or forming new spaces for new bone to form. So there is always a good equilibrium between bone formation and bone destruction among these cells. And that’s why we call the bone not a static organ, but rather we call the bone an active organ because there’s always bone formation and there’s always bone destruction.

So what myeloma does is induce the production of hormones or cytokines such as TNF and RANK ligand as you see in the right side, that activates these osteoblasts and they start chewing up or destroying more bones. Where in the left side there is an inhibition of bone formation. So there is disturbance of that equilibrium towards more destruction. And it is in this destruction that myeloma cells can proliferate and a vicious circle is set, to the point that when there is more bone destruction there is more capability for the myeloma cells to grow and to proliferate and it’s in this vicious circle that we have to learn how to stop it.

A great advance in this process is not only the therapy that can destroy the myeloma to revert the equilibrium to normality, but we have new molecules that can actually block these inhibitory factors that activate osteoclasts, such as RANK ligand, and we have now a whole host of medications called bisphosphonates, that can alter the activity of the osteoclasts, reducing the bone destruction of these patients, and improving their quality of life.

Not only that, now we have evidence that the use of bisphosphonates long term may also impact in the survival of the patients, improving not only their quality of life, but also improving their general outcomes.

Slide 18: Renal Metabolism of FLCs
When we talk about active myeloma, the other organ that is usually damaged is the kidney. As you can see in this slide in red in the top left is the vascular part as the blood vessels go into the kidney, the urine or the liquid part of the blood filtrates into these tubules, where eventually it becomes urine and that’s the normal metabolism in the kidney. Unfortunately, the light chains, which are the part of the proteins that are produced liquid part of the blood filtrates into these tubules, where eventually it becomes urine and that’s the normal by these myeloma cells, overwhelm the normal ability of the tubular part of the kidney to absorb and these proteins continue to accumulate in the tubular part of the kidney, in the collection tubules, to the point they start forming casts. And those casts cause damage and eventually kidney disease.
DR. RUBEN NIESVIZKY:
There are several factors that can induce kidney disease, not only these tubules that I was telling you, but high calcium in the blood can cause dehydration, and patients who have infections or that take medications such as nonsteroidal anti-inflammatory agents, such as ibuprofen, naprosyn, etc., can damage the kidney, and therefore it’s very important for us as physicians and practitioners to avoid these types of medications in patients. In addition to avoid antibiotics that can cause kidney damage, such as aminoglycosides and, of course, avoid standard radiology IV contrast that can actually damage the kidney significantly.

Slide 19: Kidney Damage
Twenty percent of the patients at diagnosis have evidence of kidney disease and quality of life can be improved and survival can be improved, if one of the only things we do for a myeloma patient is reverse the kidney damage.

Slide 20: Abstract
But not all the news is bad. Now with the newer therapies and since the era of the stem cell transplant, there has started to be evidence that long term survival can be achieved in those patients who achieve an active or a good response.

Slide 21: Abstract
This is a recent publication by the Spanish Group in which they report that patients, after receiving a stem cell transplant, and they can maintain a complete response, can be maintained in complete response for more than 11 years, suggesting that indeed there is a cure.

It’s still premature I would say to say absolutely that there is a cure, but I think now there is a subpopulation of patients that can enjoy complete responses for more than ten years and those would be the people who eventually would be cured.

So the field has to be advanced, not only in the supportive care, talking about kidneys, talking about bone, but the field has to be advanced also in our ability to eliminate any minimal residual disease in the patients and treating myeloma.

Slide 22: Treatment in MM Patients
So what are we going to be talking today about? These are mostly the objectives of our talk. What is the goal of the treatment of multiple myeloma? What is the best induction therapy? How to individualize therapy. Is there any role for maintenance? And is there any role for the new drugs?

Slide 23: Treatment of Elderly MM Patients
So let’s talk first about the goal of the therapy.

Slide 24: Quality of the Response/Survival
Let me walk you through this slide. Here you see a plot of four curves. If you look at the flat line at the beginning in red, that’s the level that indicates the survival of the patients. So as you see, 100%, in this evaluation, at the beginning, there is 100% survival. Here is actually progression-free survival, so it only
DR. RUBEN NIESVIZKY:
indicates how many patients on this analysis remain in response without progression of their myeloma. And there are four curves, the bottom curve shows people who only achieve a partial response with therapy, and in the top you can see the green line, which indicates all those patients who actually not only achieve a complete response, but with the best technique for minimal residual disease, what we call immunophenotypic complete response, remain without progression. And clearly, if you advance through the months, there is clear evidence that the more robust is your response, the less a chance for progression of disease occurs. And therefore we and others are in the belief that not only achieving a very robust response, what we call a conventional complete response or a stringent complete response, is necessary to achieve a long term outcome.

Slide 25: CR should be an Important Objective
Certainly we all have seen patients who have only achieved a partial response and have lived a very long time, so maybe we don’t know all the truth about this issue, but in general the field is moving to what’s the concept that complete response should be an important objective in elderly and also in young patients with multiple myeloma. But we have to always remember that achievement of the response has to be a high quality and has to be sustained and has to allow acceptable toxicity because the patients need to tolerate the therapy.

Slide 26: Treatment of Elderly MM Patients
So how to get there? What is the best induction therapy, how do we get there? So for many years, as I told you in the first slide, before Coca-Cola proved to be superior than urethane, the next best drug was melphalan and prednisone, what we call MP.

Slide 27: MP: No Longer an Option
And right now I can tell you now that MP is no longer an option. Forty-two percent survival at three years is unacceptable to us.

Slide 28: Thalidomide
And as the 21st century came in, we learned more about thalidomide. Thalidomide, a potent inhibitor of growth factors, that stimulate myeloma cells, that decrease the addition of the myeloma cells to their bone marrow context and their bone context, that you can see in this micro-photography. The myeloma cells are surrounding an elongated cell, which is an endothelial cell. This endothelial cell is a permanent component of the bone marrow. And the plasma cells are all surrounding it. If this would be a nursing cell, these cells actually nurse and feed these myeloma cells. Actually in the test tube you can remove these plasma cells out of this context, they will die. These cells, myeloma cells, require the attachment and the union of the marrow micro-environment or neighborhood to live.

So these drugs such as thalidomide or lenalidomide have the ability to interfere with that reaction and then allow the cells to die. Another effect that the thalidomide and the immunomodulator drugs will do will be to decrease the formation of blood vessels, the proliferation of endothelial cells, as you can see here, and it will increase the cancer surveillance by T cells and that’s why they’re called immunomodulators.
Slide 29: MPT vs MP: Efficacy
Now we have learned much more about activity of these agents, but a plain reason why these agents work or don’t work in all the patients is still not understood. But what we do know, that adding the thalidomide to the melphalan and prednisone background – as I said, melphalan-prednisone is no longer an option – now adding the thalidomide, it is proved to improve response rate, progression-free survival and overall survival in at least three different clinical trials. And there was also some benefit in other trials.

Slide 30: MPT vs MP: Toxicity
The problem, as you see in the bottom of the slide, that if you put everything together, the overall survival was not significantly improved, putting everything together, probably because thalidomide cannot be maintained long term in most of the patients, there a degree of discontinuation, that it’s too dependent on the side effects, which include neuropathy, somnolence, constipation, thrombosis, etc., as you can see in this slide. Increased infection rate, thrombosis and discontinuation.

Slide 31: Lenalidomide
So the best next thing was lenalidomide, a better immunomodulator drug, more potent, and with less toxicity, less neuropathy, less constipation, less neurological effects, less somnolence. But the only problem was that this drug did produce lower blood counts.

Slide 32: Lenalidomide +/- MP
Recently it has been published already that the combination of lenalidomide, which is called MPR, with melphalan and prednisone, is superior to melphalan and prednisone, only when lenalidomide is used as some maintenance.

So this is the design of a clinical trial. Remember I told you at the beginning, we must use clinical trials to prove that something works. So in this clinical trial there’s three groups. In the bottom is melphalan and prednisone, which we call the control, which is used as an induction, and the followed by placebo as a maintenance. So nothing or sugar pill as maintenance. In the middle is the MPR, which is the combination of melphalan, prednisone and lenalidomide. But it is given only for nine cycles, nine months basically. And then placebo as maintenance, sugar pill as maintenance. And the third, which is the one in the top, which is melphalan, prednisone and lenalidomide, followed by lenalidomide maintenance.

Slide 33: Response & PFS: MPR-R vs MP vs MPR
And as you can see in the result again, remind you of how the curves looked, the yellow line indicates how the people who get the MPR followed by the R maintenance survived free of relapse or progression-free survival, longer than those who received either melphalan and prednisone or those who received melphalan, prednisone and lenalidomide without maintenance. And as you can see, the curves separate at cycle number 9. And what makes the difference then is not the combination of the lenalidomide with the melphalan and prednisone, but rather the absolute positive effect that lenalidomide is doing here as a maintenance.

So with this evidence we can only say that lenalidomide advanced the field in that we can protect against relapse by using it as maintenance.
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Slide 34: Introduction  
So then I will walk you through another clinical trial that we introduced now almost ten years ago, as the BiRD trial, in which we combined lenalidomide, dexamethasone and an antibiotic called clarithromycin, which used to be called Biaxin®. So we treated more than 70 patients on a schedule of dexamethasone once a week, with lenalidomide daily for 21 days, and clarithromycin 500 milligrams twice daily through the month.

Slide 35: Maximum Response to BiRD  
And our surprise was with this very limited amount of drugs we could achieve a complete response in 41% of the patients and out of those 41% of the patients, 79% of the patients had a stringent complete response, a very deep robust complete response, indicating a long term survival.

Slide 36: Progression-Free Survival is not Affected by Transplant After Lenalidomide  
And indeed in a more recent update by my colleague Dr. Rossi in the American Society of Clinical Oncology, has demonstrated that the use of a BiRD therapy, achieved progression-free survival in the same trend than transplant after induction. Which doesn’t prove yet because it is not a randomly assigned trial, but it suggests that a randomized trial should be done, testing these two modalities to ask the question whether there is an improvement of survival. But we are very optimistic that using this combination as a backbone, and adding newer drugs, can eventually achieve a maximum response.

And I will tell you about some things we are doing in the future with that type of platform.

Slide 37: Bortezomib  
But not to forget the first in class agent, from the proteasome inhibitor family, which is called bortezomib. This drug actually was tested scientifically first, in the bench, in the test tube, proving that it can kill myeloma cells in culture. And then in animal models. And eventually was taken to the clinic in Phase I, Phase II and Phase III. In a dramatic short time, less than five years, that drug was developed and showed fantastic results.

Slide 38: VISTA: Velcade as Initial Standard Therapy  
This took us to another trial to prove that this drug can in fact improve the survival of patients who are elderly, more than 65 years old, in this VISTA trial, in which they compare randomly assigned patients to receive bortezomib, melphalan and prednisone, versus melphalan and prednisone. The primary endpoint was time-to-progression, but there were other endpoints, such as overall response rate, duration of response, overall survival, progression-free survival, and quality response.

Slide 39: OS (ITT)  
And although this is now a classic curve and has been sub-analyzed and followed up, it still proves that overall survival can be achieved by the combination of these three drugs with a 30% reduced risk of death with the three drugs.

So I think I have given you enough information to prove that melphalan-prednisone is no longer a good combination, but that we have novel agents that must be used rather than that initial. But not without cost.
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Slide 40: Grade 3 / 4 Adverse Events
We do have some level of toxicity, such as peripheral neuropathy and gastrointestinal toxicity with the use of bortezomib, and there is other strategies that we need to start to learn, to how to modify that toxicity. Because it may alter the ability to give the drug properly.

Slide 41: UPFRO N T Protocol
This we learned with another clinical trial, that we are analyzing here in the United States, more than 500 patients have been treated in this randomized trial, in which we compare bortezomib-dexamethasone versus bortezomib-thalidomide and dexamethasone. And the bottom, the group that received bortezomib-melphalan-prednisone, again all patients assigned in a random fashion, first in a more intense induction, followed by a maintenance.

Slide 42: Patient-Reported QoL
And as you can see the results, the response rates and so far the progression-free survival in the three arms is very similar. But in patient-reported quality of life, this is one of the only trials that has actually looked at this systematically and very carefully, we can see that the use of bortezomib and dexamethasone or the bortezomib-melphalan-prednisone, are much better tolerated than the use of thalidomide-bortezomib and dexamethasone. So if there is no improvement in progression-free survival in the three arms, but the bortezomib-dexamethasone gives you better quality, it is clear which one are we going to be using for our patients. Mostly for those patients who are elderly.

Slide 43: Treatment of Elderly MM Patients
And the question I have for you then is, is it possible to individualize treatment, because not every myeloma is the same, not every patient is the same.

Slide 44: Functional Assessment
So we have to start learning not only the molecular characteristics of each patient, but we have to learn the molecular characteristics of the disease, and the background in which each patient is living. It’s not the same thing, a patient who is sleeping and not active as a grandmother who’s able to do these types of exercises.

Slide 45: Once-Weekly Administration of Bortezomib
And we have learned, for instance, with once weekly administration of bortezomib, the degree of neuropathy significantly decreases. And the discontinuation rate clearly decreases. In this graph you can see how patients treated with a classic twice per week have a peripheral neuropathy, severe peripheral neuropathy in about 14% of the patients. And when you give the drug once a week this drops to 5%. And this has been already compared in different studies. And also the rate of discontinuation drops to half, from 34% to 17% to 12%.

Slide 46: Once-Weekly Administration of Bortezomib
Again, if we are able to maintain the dose longer and keep the patients longer on the bortezomib once a week, that may result in better clinical outcomes. And as you can see in the top, you see the old way to give it, twice per week, and how it compares with other regimens in which they give the bortezomib once a week.
DR. RUBEN NIESVIZKY:
Indeed, giving it once a week, you have a better response rate and you have a longer progression-free survival and an overall survival of improvement, which indicates if you can give the drug longer with less of discontinuation, you will be able to maintain the patients and have better outcomes. So we have to be always very cognizant of the toxicity that a drug can give before we can continue indicating its use.

Slide 47: Bortezomib IV vs SC
Thanks to the French, we have already learned not only that the use of once a week is superior, but also now we have learned that the use of subcutaneous bortezomib is exactly the same in terms of efficacy as giving it intravenously, in that you can achieve the same overall response rate, the same CR rate, and the same time-to-progression, and yet the toxicity that is associated with subcutaneous is way less than when you give it intravenously in the context of peripheral neuropathy. You have less peripheral neuropathy when you give it subcutaneously than if you give it intravenously, which allows us again to give the drug for longer time and eventually allow patients to have less suffering with the drug.

Slide 48: Treatment of Elderly MM Patients
We’ll talk a little bit more about maintenance.

Slide 49: MPR-R vs MPR
Just to make emphasis in that the continued use of lenalidomide can take us to better progression-free survival and hopefully eventually improvement in overall survival. There is now a CALGB, American study, that has shown that post-transplant, continued lenalidomide post-transplant, can increase the overall survival. And we hope that we have already set up the stage for using bortezomib as a maintenance drug, that will eventually be tested equally and we perhaps will learn that can also be an excellent option as maintenance drug in multiple myeloma.

Slide 50: Treatment of Elderly MM Patients
Let’s talk a little bit about what drugs are in there. And I tell you there’s many drugs that are around, but it is very important to test these drugs. And it’s extremely important, I cannot make enough emphasis, that if there is a possibility, always try to participate in the clinical trial.

Slide 51: Preparing Patients for a Clinical Trial
A clinical trial not only will advance the field, but will allow you to receive the best drug with the best attention. Patients, it’s well demonstrated, patients on clinical trials, either Phase II, which are not randomized or there’s no placebo involved, or either Phase III, which there is a comparison, will have better treatment, better care than those patients who are not on clinical trials. So always try to get in a clinical trial. If you’re a practitioner, try to introduce the concept early, try to recommend the patients early on in their evolution, contact the investigator to review the inclusion and exclusions early, whenever is possible, do not start another agent before the patient can be screened for study because that may eliminate a possibility of using drugs early in their disease. Always try to refer them to a center in which they have the ability to give these type of
DR. RUBEN NIESVIZKY:
drugs. And remember that not only you have better possibility of receiving better care, better screening, better support, but also some of these drugs are given for free, when they are involved in a study. And some studies even cover expenses of the administration or the traveling, etc.

Slide 52: Novel Agents
As introduction of novel agents, we have two new drugs coming down the pike. Carfilzomib just recently approved for the patients who are relapsed or refractory after three lines of therapy. They have had to be receiving or relapsed after immunomodulatory drugs and a proteasome inhibitor, probably bortezomib. Or pomalidomide, which is now in Phase III clinical trials. Those agents, even as single agent, have great activity.

And we have other agents, as you see below, vorinostat, panobinostat, elotuzumab, perifosine and bendamustine, that perhaps don’t have a great activity as single agent, but in combination appear to enhance the activity of the disease. So we are all very excited in the combination of these drugs.

Slide 53: Proteasome Inhibitors in MM
For example, we have several proteasome inhibitors. As you know, bortezomib has gone through accelerated FDA approval and it’s used perfectly now in several lines of therapy, first line, second line, etc. Carfilzomib now has gone through Phase I and Phase II. Phase III has been concluded. And now it has been already approved, even without having the complete information of a Phase III trial. And they have other proteasome inhibitors such as marizomib. The ones that I’m indicating here, like oral drugs, such as MLN9708 or the ONX0912, which will allow for longer, more active use, as indicated here.

Slide 54: Future Directions: CRd Frontline
Just to give you a glimpse, my colleague from University of Chicago started this trial when he was in University of Michigan, Dr. Andre Jakubowiak, in which following our initial testing of carfilzomib, lenalidomide and dexamethasone in relapsed and refractory, he tested these in Phase I and Phase II, non-randomized fashion, to patients front line. And as you can see here, the response rate is staggering. You have a CR rate of 53%, is unheard of, even in the absence of stem cell transplant.

So we are confident that the field is moving towards that goal of cure.

Slide 55: Pomalidomide
So do we have other drugs down the pike? A third generation of immunomodulators, in this case pomalidomide, which has features, molecular features very similar to thalidomide and lenalidomide. It is a distinct immunomodulatory agent, has direct anti-myeloma activity, has significant anti-proliferative activity in the test tube and in the animal models. And has certainly activity in relapsed and refractory patients.

Slide 56: Response to Pomalidomide/Dexamethasone
As you can see here, a list of all the clinical trials, we have seen with pomalidomide, from top to bottom, we see tested in patients who have lesser prior regimens, we have response rates of 60%. And in patients with double refractory, that meaning not responsive to proteasome inhibitor such as bortezomib or lenalidomide, have a response rate of about 30%.
Slide 57: ClaPD Study Design
In the same context, we have done similar trials. We have combined pomalidomide in the same construct as the BiRD therapy. As you see, clarithromycin, 500 milligrams twice a day, dexamethasone once a week. But this time in patients who have all gone through lenalidomide or bortezomib.

Slide 58: Treatment History with Len/Bort
And as you can see here, even patients who are refractory to lenalidomide and bortezomib, we can achieve with this combination a 60% response rate. And we’re going to be updating this in the upcoming ASH, where Dr. Tomer Mark, who is my colleague and partner, will report the updated results in a much larger population.

Slide 59: Summary/Conclusion
So as a summary, I could tell you that the novel agents, in combination with melphalan-prednisone compared to conventional chemotherapy alone, are superior. That complete responses should be a goal, but we require dose adjustments, we require a more individualized therapy. We also remind you that maintenance therapy with bortezomib or lenalidomide suggests possibly an improvement in response rate and progression-free survival. And we require longer follow-up and new clinical trials to definitively define the benefit of maintenance therapy. And certainly we need evaluations, better way to evaluate quality of life. And the future is bright as numerous planned and ongoing studies will answer questions with newer drugs.
And this concludes my presentation. Again I thank you very much for your attention. And I’ll be happy to answer questions.

Slide 60: Question and Answer Session
LAUREN BERGER:
Thank you so much, Dr. Niesvizky, for such an informative presentation. It is now time for the question and answer portion of our program.
We’ll take the first question from the web audience and Greta asks, is it possible to start treatment too soon? I was asymptomatic when I was diagnosed, but my IgG was 4739. I had a stem cell transplant, but didn’t achieve remission. The disease is considered stable and I am now on maintenance therapy. If I started treatment too soon, did I hinder my chances of reaching remission?

DR. RUBEN NIESVIZKY:
Absolutely not. I think that there’s many factors that need to be considered. The initiation of therapy is not only dependent on the symptoms of the patient, but in the presence of the CRAB criteria. So there should have been some alterations in the CRAB criteria to initiate therapy. Sometimes I have even treated patients without CRAB criteria, again, the hypercalcemia, the renal dysfunction, the anemia or the bone disease, based on the rapidity of the protein to go up. So if I see a protein going up very fast or I have another parameter that will induce me to start therapy, I will ask the patient to start therapy early. So I don’t think that starting treatment early hinders response. I think that response is more dependent on inherent biological and clinical aspects. And as I said, one of our goals is to achieve complete response with newer therapies, but many
DR. RUBEN NIESVIZKY:
patients do not achieve a complete response and many patients can live longer even without achieving a complete response. So still we don’t understand why some patients can continue living longer even without achieving a complete response.

LAUREN BERGER:
Thank you. We’ll take the next question from our telephone audience, please.

OPERATOR:
Our next question comes from Henry in Missouri. Your line is now open.

HENRY:
Yes, Doctor, you talked about bone disease. And I had a question in regard to the different types of bone disease. Like most information I’ve seen shows that patients come down with lytic lesions from the bone disease. What is your experience in regard to patients that initially have lytic lesions and after treatment of many years with Zometa® and other treatments, then they start developing the osteoblastic, they’ve been called, lesions?

DR. RUBEN NIESVIZKY:
Eighty percent of patients with multiple myeloma will have some form of bone damage. Certainly not all the time it’s manifested by lytic lesions, sometimes it’s just brittle bones and that’s caused by lack of mineralization of the bones and that’s called osteoporosis or osteopenia. The mechanisms by which some people get osteolytic lesions and some people get just osteopenia is not perfectly understood. It’s just that they always go hand in hand. And fortunately we have been able to arrest the progression of lytic lesions by using other therapies that you have mentioned, and unfortunately very few agents can actually form bone. The only agents that have actually shown to form bone is bortezomib or the proteasome inhibitors. None of the other agents have actually shown to form bone. What we call osteoblastic is the fact that there is some new bone formation in those areas. Extremely rare in myeloma, but in prostate cancer or in other types of cancer, instead of the bone lesions being destructive, what we call osteolytic lesions, they are with a new formation of disregulated bone, what we call osteoblastic lesions. We doctors use this type of jargon very often and I would encourage you to clarify with your physicians what do they mean by osteoblastic. But usually we can see something when there is some form of response, some new mineralization, but that’s not commonly seen every time.

LAUREN BERGER:
Thank you for the question. The next question comes from the web audience from EJ. Can you please tell us what criteria determine a complete response and does this vary among different treatment specialists?

DR. RUBEN NIESVIZKY:
There’s already published a common criteria for response, but you’re right, this is a moving target. So the better is our technology to detect minimal residual disease and the more generalized we have these studies,
DR. RUBEN NIESVIZKY:

we’ll be able to refine the definition. Currently the one that we are using is International Working Group criteria, which includes two forms of complete response – SCR, which is stringent complete response, and CR. And they just differ between both is that one we use immunohistochemical or immunological techniques to detect minimal residual disease in the bone marrow, and the free light-chain in the serum has to be normal. But in both cases we should see no remnants of disease by serum protein electrophoresis in the blood and in the urine. Then we have a category called PR, which is partial response, which is 50% drop on the protein or in the M-spike both in the blood and the urine, without new bone lesions or new plasma cytom as, which are myeloma tumors. And in between the complete response and the PR, we have what we call the VGPR, which is a 90% drop on that tumor marker, the M-Spike, either in the blood or in the urine. But I cannot go through all the categories, but it’s already well published and you can just Google it, IWG criteria.

LAUREN BERGER:

Thank you, EJ, for your question. We’ll take the next question from the telephone audience, please.

OPERATOR:

Our next question comes from Shannon in Minnesota. Your line is now open.

SHANNON:

Hi, Doctor. Thank you so much for your time and thank you for dedicating your life to this disease. I was just wondering, is there anything that we can do diet or exercise-wise that will dramatically impact how well we’re doing with the disease?

DR. RUBEN NIESVIZKY:

It’s a slippery slope because many times you will hear that eating less of this or more than that will be better for you. And the only thing I can tell you, that the only thing that has been proven is that a healthy, well-balanced diet is the way to go. You have to talk to your doctor at the given time, depending on what type of therapy you’re getting and what dietary modifications you may need, depending on your symptoms. For instance, if I have a patient receiving high-dose dexamethasone or corticosteroids, I want to eliminate a possibility or reduce a possibility of developing diabetes mellitus. So what I do is I ask the patients to follow a low carb diet during that time. And their well-being will be increased and they will reduce the possibility of having sugar problems. I would also urge everybody to hydrate themselves, which is increase the oral intake of fluids, which should be water, at least eight glasses of water, or decaffeinated low carbohydrate type of drinks. Probably the most natural are the best, but the important thing is just to continue well hydration to avoid all the toxicities that the drugs can induce and also the problems that the calcium can produce. But I cannot tell you which supplement is favorable or not because there’s no proper scientific studies to show one or the other. You will hear a lot about taking high dose of Vitamin C or hearing about supplements. And I urge you that if you’re going to take supplements, please clear it with your physician because we don’t know what potential interactions this can have with your medications, and can reduce the effect of the medications giving benefit.
LAUREN BERGER:
Thank you for your question, Shannon. We’ll take the next question from the web audience and Roman asks, does foot neuropathy go away? I had chemo for four cycles and the last cycle it hit me like a brick and it has not gone away since January when I finished my chemo.

DR. RUBEN NIESVIZKY:
A lot of it depends on what the origin of the neuropathy. You have to understand that many patients with multiple myeloma have already an underlying neuropathy, sometimes subclinical, which means without symptoms from the beginning, but if we do very sophisticated nerve conduction studies we can actually see that many of those patients already have some form of nerve damage in association with multiple myeloma. Now we recognized that medications for multiple myeloma can cause neuropathy. The most famous of all of them is thalidomide. Thalidomide had been shown to have neuropathy and unfortunately irreversible, which is one of the causes that people had to discontinue and that’s why we had so many discontinuations. That’s one of the great advantages of lenalidomide and pomalidomide, we have lesser neuropathy. We have to watch for neuropathy with these agents, in a lesser degree. The other one is bortezomib, which also causes neuropathy. And by careful monitoring of the neuropathy early on its use, we can reduce the dose or interrupt it, as the package insert suggests, and reduce the incidence of neuropathy. Most of the neuropathy induced by proteasome inhibitors is completely reversible. If not 100%, 80 or 70%. That would allow you to resume therapy at a lower dose or lower intensity. Many times we have already interrupted the dosing of the four cycles and we see neuropathy getting worse, but eventually that neuropathy will improve. There are many medications that can help you with the symptoms, while we allow your nerves to heal themselves.

LAUREN BERGER:
Thank you for your question, Roman. We’ll take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Joyce in Ohio. Your line is now open.

JOYCE:
Yes, Doctor. It was a very good presentation you gave. I have multiple myeloma and when it started off they found it in my back, which I had radiation for. Now my doctor has me on Velcade® and I’d like to know if that is one of the medicines that can help my myeloma or do you have another choice?

DR. RUBEN NIESVIZKY:
Well, each case is individual. I cannot comment much on your particular case. But certainly bortezomib, which is the one that you’re getting, is a fantastic drug and has a great track record. We have plenty of information of how to use it in the relapsed setting. And what we are using right now is not only alone, but we’re using it in combination. We have learned that in combination with lenalidomide or in combination with chemotherapy, the responses can be enhanced and the quality of life is not as modified. And also could be used long term. If we use it subcutaneously or if you’re using weekly, you can modify the dose for better benefit. So yes, it’s a great drug. It’s a great advantage. And as long as you’re monitored well, you can always add to it. It’s one of the most novel medications because allows a lot of combinations with it.
LAUREN BERGER: Thank you for your question, Joyce. We’ll take the next question from the web audience and this question is asked by Amy. My mother was recently diagnosed with very early stage multiple myeloma and her doctor has recommended only drug therapy, lenalidomide, at this point. He suggested that stem cell transplant would not be called for at this point. Do patients who have stem cell transplant early, as opposed to lenalidomide or some other drug therapy, do they generally have a better outcome?

DR. RUBEN NIESVIZKY: No, lenalidomide is a good agent to start with, and as you saw with our BiRD trial, in combination with dexamethasone and clarithromycin, gave very good front line results. And there is an ongoing clinical study, directed by the Dana-Farber in Boston, in collaboration with the Intergroup in France, comparing the combination of lenalidomide, bortezomib and dexamethasone induction, followed by transplant, versus just the drugs. And we don’t know the results of that one actually. We are anxiously awaiting for those results to answer your question, whether transplant up front is superior to just drugs. Right now many of the transplanters in our field are saying that transplant is more a choice rather than a necessity. We are waiting for the results of these clinical trials. I can walk you through clinical trials that were done about 12 years ago in which they showed that doing a transplant early or doing a transplant late did not benefit the survival, there was no difference of survival. There was only advantage in the time without symptoms for those patients who actually got transplanted. In other words, if you get a transplant early, you will enjoy more time without symptoms, but that won’t necessarily result in higher survival. Unfortunately we cannot use these studies any more because those studies were done before the existence of thalidomide, lenalidomide or bortezomib, so we need to revisit and we are waiting for those results.

LAUREN BERGER: Thank you for your question, Amy. We’ll take the next question from the telephone audience, please.

OPERATOR: Our next question comes from Marguerite in California. Your line is now open.

MARGUERITE: Doctor, I’ve taken many treatments and I’ve been a survivor since ‘05, 2005. Now I’m on dexamethasone and lenalidomide, which is Revlimid®. I’m off Revlimid now for ten months, but my protein’s going up. But the question I have for you is I noticed with the dexamethasone that my right eye gets blurry and hardly can see out of it, for the last six months, I’ve been mentioning it to my doctor, but nothing seems to be done. It’s affecting my eyesight. I do have glaucoma, but my eye doctor said everything’s fine. So do you recommend another steroid that I could take that would be less or that still helps the myeloma, but will help my condition of this side effect?

DR. RUBEN NIESVIZKY: Yes, all the steroids are good for myeloma. And all the steroids are also bad for the eyes. Most of the time the alterations in the eyes are caused by weakening of the muscles of the eye, which is completely reversible. So this inability to focus or problems with distant eyesight, may improve once you stop the steroids. However,
DR. RUBEN NIESVIZKY:
There are other things that the steroids can do, such as cataracts. So what I ask my patients is always to go to the ophthalmologist and see if they have cataracts. Many of the patients will require cataract correction surgery, which is in general very simple to do. And the patients welcome very much this type of surgery. Very rarely I see glaucoma or changes in the eye pressure that need to modify the corticosteroid. So in general all corticosteroids are good for myeloma, but they will have some problems with the eyes. But most of them can be corrected or reversible.

LAUREN BERGER:
Thank you for your question, Marguerite. We’ll take the next question from the web audience and Kathy asks, what about younger patients, do the topics today focus primarily on older patients? I am a 50-year-old patient.

DR. RUBEN NIESVIZKY:
The 50-year-old patients are the most rare patients. The great majority of our patients are in the seventh or eighth decade of life. The goals, however, remain the same. I think we all agree that the younger patient requires aggressive therapy to achieve the complete response. You can achieve a complete response with two or three drugs, depending on what your doctor thinks is appropriate. Also depending on your cytogenetic risk factors, that your doctor will know exactly what to obtain to define them. And we can say the same about transplant. If you can achieve a complete response or near a complete response or a very good partial response, without a transplant, we are still awaiting the results of that clinical trial that will let us know whether transplant is necessary or not, but certainly we will do transplant in those patients who are fit, younger and can sustain this type of therapy. And after the transplant there is still the controversy whether everybody will require maintenance, but maintenance in general is positive treatment for the younger that you are. So in general the goals are the same, the drugs are the same, it’s just the regimens may change a little bit.

LAUREN BERGER:
Thank you for your question, Kathy. We’ll take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Wanda in Michigan. Your line is now open.

WANDA:
Hi, Doctor, thank you so much. Very informative. I have a problem, I had a stem cell transplant approximately two years ago. I have excessive, extreme itching and I don’t know if it’s from the multiple myeloma. I’m on no maintenance therapy whatsoever. But I did have nerve damage in one of my eyes and I just had to go through cataract surgery. But would this itching be anything from the multi-myeloma? Oh, and the hot flashes with the itching.

DR. RUBEN NIESVIZKY:
The answer is that we don’t have an easy answer about the itching because there are many reasons for itching. It could be local skin problems, medications, could be liver, could be kidney. There are many ways to
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DR. RUBEN NIESVIZKY:
investigate itching, but fortunately that’s something that your doctor is equipped to diagnose. Certainly we have many ways of treating itching, again with local creams and ointments and also with medications. So it’s in general not associated with multiple myeloma, very rare occasions. The way that you describe your disease, it doesn’t seem that it’s because of the multiple myeloma, but I think your doctor can easily determine that.

LAUREN BERGER:
Thank you for your question, Wanda. We’ll take the next question from the web audience and Sherry asks, how can someone living in a remote or rural area and unable to travel, how can they get the best available treatment and research advances in their home community, how can their community physician link up with the treatment or research center?

DR. RUBEN NIESVIZKY:
That’s a fantastic question and it’s going to become more relevant as our medical field advances and with new economics. Certainly there should be a local oncologist able to manage the general aspects of multiple myeloma. And many centers are trying to network through the communities to bring out newer drugs. That being said, there should be a constant communication between the local oncologist and the myeloma specialist to be able to refer patients to clinical trials and get proper medical care. That being said, we have successfully brought clinical trials into the community, in that slide that I showed you, the three agents, over 500 patients. So it’s something that is pretty doable. Newer agents, when the disease has relapsed many times, are only available in centers, unfortunately, and for that reason patients should be referred and transportation should be provided. Now in the 21st century, your doctors, your local doctors have the ability through emails, through webcasts, through networks, through The Leukemia & Lymphoma Society and other organizations, to reach one of us investigators in myeloma and get a pretty good idea of how to manage each case in the community.

LAUREN BERGER:
Thank you for your question, Sherry. We’ll take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Nancy in Michigan. Your line is now open.

NANCY:
Hi, thank you for taking my call. I was diagnosed in March of 2011 and went through Velcade and dexamethasone regimen and then had a stem cell transplant. And so currently I’m in remission. But I’m not on any kind of maintenance therapy. Should I be on maintenance or should I wait for symptoms to reoccur? Thank you.

DR. RUBEN NIESVIZKY:
Very good question, very difficult to answer. And that depends a lot on what the doctors saw when you presented. And particularly the nature of your disease, the cytogenetics. It’s a big controversial issue. If you are
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DR. RUBEN NIESVIZKY:
in complete response, some people believe that you should enjoy the complete response without medications. Some other people, in response to the clinical trial from the CALGB, that suggests that maintenance improves the survival of patients regardless of the response, should be maintained in lenalidomide. So that would depend a lot on the characteristics of each patient. I can tell you most of my patients now are getting maintenance lenalidomide, some of them get maintenance lenalidomide and bortezomib, very few don’t get maintenance. And we need more solid evidence from clinical trials to give you a general recommendation. So I would trust your doctor in defining in your case what’s the best set. Again, I don’t know, you are going to be actually in better shape if God forbid the disease comes back and that you will be able to receive therapy second line and third line, so I wouldn’t despair that you’re not getting maintenance. That’s my answer.

LAUREN BERGER:
Thank you for your question, Nancy. We’ll take the next question from the web audience and Daniel asks, can you talk about secondary cancers with Revlimid maintenance?

DR. RUBEN NIESVIZKY:
Very controversial, very hot issue right now. Let me just say to start with is that we know about secondary cancers in multiple myeloma since the 1960s. It’s been a problem with myeloma since then. So the emergence of secondary cancers is not a new problem. It’s a problem that has existed all along. It had been neglected since then because most of the patients will die with myeloma during the 60s and the 70s, so it was basically moot because we didn’t have good treatments for multiple myeloma and the best agent against multiple myeloma then being melphalan or other alkylating agents, are well known to produce leukemias, myelodysplastic syndromes or secondary cancers. So the same you can say about radiation therapy. So doctors that are old enough to have passed through those years will understand that patients who get radiation therapy and that get chemotherapy, particularly with melphan, are at high risk of developing these type of cancers. But if you just check patients who have been not treated with multiple myeloma or monoclonal gammopathy for undetermined significance, even those patients have higher risk of developing other type of cancers. So there is a background there of increased secondary cancers. Now it is obvious that if you have longer survival after you have achieved complete response, you’re going to have a higher risk of developing cancers of the elderly. So if you live to reach 60s or 70, then prostate cancer, breast cancer, lung cancer for the smokers, will also occur more frequently, just because we’re living longer. So one of the things that we have seen is that with novel therapies, people are living longer and yes, they’re developing newer form of cancer. But yet there is still not completely understanding to what extent the newer medications are enhancing that. It is my observation, though, that people on lenalidomide alone who are continuously treated with lenalidomide, do not have more incidence of secondary malignancies when you compare with a normal age-matched population. The only ones who have actually seen increase are those who get the sequence of chemotherapy, which means melphalan or adriamycin or agents like that, followed by lenalidomide. Or those who actually received lenalidomide in combination with the alkylating agent. So we are actively studying what happens with the stem cells in people who get the combination or the people who get the sequence. So yes, it is a concern, but there are many factors that have to be taken into consideration when you use these drugs.
LAUREN BERGER:
Thank you for your question, Daniel. We’ll take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Judy in Kansas. Your line is now open.

JUDY:
I have taken Revlimid for five years. I’ve had multiple myeloma since 1998 and I’m now in a stringent complete response. And my Revlimid was discontinued five months ago. However, since the day I started it I’ve had violent diarrhea. I’ve been under the care of a gastroenterologist and he has put me on opium to control it and it does control it. But since I’ve been off for five months, how long will this side effect continue, will I ever get over it? Thank you.

DR. RUBEN NIESVIZKY:
Very relevant question, again, because we see that long term lenalidomide is complicated by gastrointestinal symptoms, particularly diarrhea. We don’t understand why it does it. But it’s a frequent problem. Some people have suggested to take not only medications that can slow the bowel such as loperamide or atropine-like or even opium as you said, but also medications that can actually increase the bulk, such as Metamucil or fiber, to help you deal with that. Also we recommend to reduce the amount of dairy products or take enzymes such as lactate to try to eliminate the lactose effect for people who are lactose-intolerant. Some people have also suggested to use some medications such as colestipol, that can actually bind to the feces and reduce the amount of diarrhea. We have sometimes to reduce the dose of lenalidomide and even eliminate it. And as in your case, it persists for a while. But eventually it will get better.

LAUREN BERGER:
Thank you for your question, Judy. We’ll take the next question from the web audience and Debbie asks, I have rheumatoid arthritis also with multiple myeloma. I took Enbrel® before my diagnosis. Now my doctor says no way can I ever take Enbrel again. What are your feelings?

DR. RUBEN NIESVIZKY:
No research exists about the rechallenge of Enbrel. Certainly myeloma has been reported in people who use Enbrel and other plasma cell dyscrasias. But we don’t have enough research to answer. So the quick answer to your question is no, I would not do Enbrel, I would try to use other type of medications to try to adjust the rheumatoid arthritis. And fortunately there’s many other ones, not in the same class, but there are other medications that can help rheumatoid arthritis patients.

LAUREN BERGER:
Thank you for your question, Debbie. We’ll take the next question from the web audience. I have multiple myeloma and have a family history of the disease. I am interested in genetic studies. What can you tell me about inheritance of multiple myeloma?
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DR. RUBEN NIESVIZKY:
Fantastic questions, one after the other. We know little about it. There is a registry that has been initiated, looking at families. Certainly families with myeloma are more anecdotal than the rule. It’s not a common encounter, but we all can talk about many patients who actually carry association with monoclonal gammopathy of undetermined significance or other forms of lymphomas or myeloma. So there is some clustering. We don’t understand exactly the genetics behind it because we don’t understand what’s the background that is required for the development of multiple myeloma. We are now doing more in-depth studies to look at particular genes and now that we have the ability to interrogate the human genome, I’m confident that we’re going to be able to answer those questions. But right now we don’t know exactly who’s at risk or not.

LAUREN BERGER:
Thank you. We’ll take the next question from the web audience and Rick asks, in the absence of the other four CRAB criteria, what is the role of free light-chain criteria in determining when to start treatment?

DR. RUBEN NIESVIZKY:
I would treat free light the same as a paraprotein, in that a rapidly rising level will make me consider therapy. Because some cases, the higher it is, the more toxic it will become. But I cannot generalize because I’ve seen patients with free light-chains as high as 2,000 without kidney damage. And yet some of them with as low as 50 and having kidney damage. So there’s also some inherent quality effect on the light-chain to define whether there is kidney damage or not. But the speed of its rise will make me consider therapy.

Slide 61: LLS Myeloma Resources

LAUREN BERGER:
Thank you for your question, Rick, and thank you all for your questions. We hope this information will assist you and your family in your next steps.

Also if we did not get to your questions, please feel free to call The Leukemia & Lymphoma Society Information Specialists toll-free at 800-955-4572 or by email at infocenter@lls.org. And our specialists can provide you with information about myeloma research and clinical trials, health insurance coverage, other financial assistance or other questions about treatment, so please feel free to contact them.

Please help me thank Dr. Niesvizky. We’re so grateful that you have volunteered your time with us today.

On behalf of The Leukemia & Lymphoma Society, Dr. Niesvizky and I would like to thank you for sharing your time with us today. Good-bye and we wish you well.