Slide 1: Welcome and Introductions

OPERATOR:
Hello, everyone, and welcome to Myeloma—The Latest on Research and Treatment from the American Society of Hematology (ASH®) Annual Meeting, a free telephone/web education program. It is my pleasure to introduce your moderator Lauren Berger of The Leukemia & Lymphoma Society.

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

We have over 1,500 individuals participating from across the United States and international participants from Afghanistan, Barbados, Canada, China, Greece, Guatemala, Jamaica and Sudan.

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

Now before I turn the program over to Dr. Anderson, I’d 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 fortunate to have as our presenter Dr. Kenneth Anderson, 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 with myeloma. I would like to thank him for taking the time out of a busy schedule to provide us with an update on myeloma diagnoses 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 they 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 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 to your journey to managing your life with myeloma.

Thank you, Lauren.

Slide 2: Multiple Myeloma: Update from ASH

LAUREN BERGER:
Thanks, John.

I am privileged to introduce Dr. Kenneth Anderson, Kraft Family Professor of Medicine at Harvard Medical School, and Director of the Jerome Lipper Multiple Myeloma Center at Dana-Farber Cancer Institute in Boston, Massachusetts. Dr. Anderson, please go ahead.
DR. KENNETH ANDERSON:
Thank you very much, both to Lauren and to John Walter. This is really an extraordinary pleasure for me, to be able to be here with you today and to talk about the developments that have occurred in multiple myeloma, particularly at the American Society of Hematology.

Before I do that, I would like to thank The Leukemia & Lymphoma Society on behalf of researchers, caregivers and especially patients. They have done wonders in terms of increasing awareness, education and research for multiple myeloma, including funding basic research and discovery, funding the translation of those discoveries to the bedside, funding with their therapeutic program, the production of novel medicines from laboratory reagents, and really all the way now funding clinical trial networks as well. So they are making science count for patients, and we are all very grateful to the LLS for their efforts.

Slide 3: Integration of Novel Therapy
I’m going to ask folks to please move the slides along for me if you would, to the second slide, in terms of Integration of Novel Therapy into Myeloma Management. And it reminds me to mention that we’ve been blessed in myeloma, as we have the proteasome inhibitors bortezomib, carfilzomib. We have the immunomodulatory drugs, lenalidomide, thalidomide, and these drugs have all come along in the last decade. They work in preclinical models when, in fact, conventional therapies are no longer effective, and together we’ve moved these agents from the bench to the bedside to clinical trials in relapsed, refractory, advanced and newly diagnosed myeloma, as well as consolidation and maintenance therapy. And what we can celebrate here today, after the American Society of Hematology meeting, is that we have eight FDA approved drugs. The median survival of patients is at least two to three times what it was just a decade ago. And although we still have an urgent need for new therapies, there’s much promise for the future.

Slide 4: Combinations in the Upfront Treatment of MM
So if we could move along to the slide entitled Combinations in the Upfront Treatment of Myeloma. What you can see here is remarkable progress. Starting on the left is VAD, vincristine-adriamycin-dexamethasone, which is conventional therapy. And if one moves to the right of this slide to where it says RVD, that’s Revlimid®-Velcade®-dexamethasone. And what you can see is combinations of targeted agents, Revlimid and Velcade with dexamethasone, achieve 100% response, three-quarters very good partial response and half of patients getting a complete response, simply unprecedented frequency and extent of response compared to what we would have achieved just ten years ago. So it is very exciting that we have novel agents, the proteasome inhibitors and the immunomodulatory drugs, and if we combine them we can get unprecedented results.

Slide 5: Summary of ASH 2012
So on the next slide entitled Summary of ASH 2012 is what I’d like to go over with you very quickly here. How are we going to together use these novel agents as initial treatment, maintenance treatment, and then for patients whose myeloma has returned? What is the newest information on second generation proteasome inhibitors and immunomodulatory drugs? How can we use them in combinations? Are we finally going to deliver on the promise of monoclonal antibody therapies for multiple myeloma? Finally I will talk on treatment of side effects. Now that we’re achieving such extent and frequency of response, we need to have quality of life associated with it, and there’s much progress to report there, too.
Slide 6: Impact of Novel Agents in the Treatment of Elderly Patients
So on the next slide entitled Impact of Novel Agents in the Treatment of the Elderly Patient with Newly Diagnosed Myeloma, what you can see is that melphalan and prednisone, MMP on this slide, which has been used for 50 years in multiple myeloma, has now been combined with T, thalidomide, with V, Velcade or bortezomib, and with R, Revlimid or lenalidomide, together with lenalidomide maintenance. And what’s shown on this slide is that when you add these novel agents, the immunomodulatory drugs or the proteasome inhibitor bortezomib, to melphalan and prednisone, you increase the duration of response, the median progression-free survival, and the length of time that patients live in so doing. So remarkably the addition of novel agents is really improving outcome.

Slide 7: Treatment Schedule
Now at the American Society of Hematology, on the next slide entitled Treatment Schedule, Dr. Palumbo in Italy compared bortezomib-melphalan-prednisone, three drugs, in elderly patients with newly diagnosed disease, to four drugs, the same bortezomib-melphalan-prednisone, but then he added thalidomide to induction and also had maintenance with bortezomib and thalidomide as well.

Slide 8: Conclusion
And on the next slide you can see the results that he reported in an oral session at ASH, namely that if you use the four drugs plus the maintenance, there was an increase in the five-year progression-free survival, time to next therapy, and overall survival compared to the three drug bortezomib-melphalan and prednisone initial treatment, which was very statistically significant. The major point here is that the use of maintenance, this time with a bortezomib-containing regimen, is really making a difference.

Slide 9: Treatment Discontinuation
However, this is not for all patients because, as shown on the next slide entitled Treatment Discontinuation, one can see in the center here that if you have the four drug regimen, bortezomib, melphalan, prednisone, plus bortezomib-thalidomide maintenance, there was in fact benefit, but there’s a high discontinuation rate in the elderly patient. You can see that it’s up to a third in patients over 75 years of age, who really can’t tolerate this treatment. So for now in terms of the elderly newly diagnosed patient, it’s really a three drug regimen, with maintenance.

Slide 10: Carfilzomib: A Novel Proteasome Inhibitor
Now on the next slide entitled Carfilzomib: A Novel Proteasome Inhibitor, it reminds me to celebrate together today that we have now the second generation proteasome inhibitor, FDA approved as of last summer. It’s carfilzomib, a novel chymotryptic targeted inhibitor, just like bortezomib, except it’s a different class. The extent and the duration of inhibition of the proteasome are longer than bortezomib. And as shown on this slide, there is very little in the way of toxicity, especially neurotoxicity. And because of durable responses to carfilzomib in the context of relapsed, refractory myeloma where myeloma really is not responding to anything else, there was here a response rate of 24%, duration of response of eight months, and survival in terms of years. So fortunately in July the FDA granted accelerated approval to carfilzomib, making it possible for us to
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use it now in patients to enjoy additional benefit. The full approval for carfilzomib will come from a carfilzomib-lenalidomide-dexamethasone versus lenalidomide-dexamethasone Phase III clinical trial in patients whose myeloma comes back after one to three prior therapies, and we anticipate that that will happen relatively soon.

Slide 11: VTD Consolidation Post-ASCT

Now in the next slide entitled VTD Consolidation Post-ASCT, what I want you to focus on is the center of this trial. The proteasome inhibitor bortezomib combined with thalidomide and dexamethasone, these three drugs—a proteasome inhibitor, an immunomodulatory drug, and dexamethasone used before transplant in newly diagnosed transplant candidate-eligible patients, and also used after the transplant as consolidation can achieve molecular complete responses in multiple myeloma—fewer than one myeloma cell in ten million normal cells in the bone marrow, an extent of response we previously have not been able to achieve. So this is quite remarkable, a proteasome inhibitor, an IMiD and dexamethasone before and after transplant yields unprecedented results.

Slide 12: Carfilzomib-Thalidomide-Dexamethasone For Induction and Consolidation

So if you then move to the next slide entitled Carfilzomib-Thalidomide-Dexamethasone for Induction and Consolidation, this is the exact same model, except this time what’s been done by Dr. Sonneveld in Europe and reported at ASH was, in fact, the addition of carfilzomib-thalidomide-dexamethasone to be used before and after transplant.

Slide 13: Cumulative Response

And what you can see on the next slide entitled Cumulative Responses Percentages, in the white and the red and the blue, is that the response rate in terms of the decrease in myeloma burden is markedly improved. As you use the carfilzomib-thalidomide-dexamethasone before transplant, there’s a response. When you have the transplant, that response is further heightened. And then when you use these three drugs to consolidate the response, one gets further benefit in terms of a consolidation strategy.

Slide 14: Conclusions

So on the next particular slide entitled Conclusions is a summary that carfilzomib, having been approved in advanced myeloma, has been combined and used earlier—carfilzomib-thalidomide-dexamethasone being used as initial and as a consolidation treatment. And on this slide of conclusions, you can see that it’s markedly effective, since the response frequency increases with time, with the transplant, and with the consolidation. And in fact you can readily harvest peripheral blood stem cells for transplant. So just like bortezomib and lenalidomide, so it will be with carfilzomib. They were all initially approved in advanced myeloma, but they’re moving to the initial management.

Slide 15: CYCLONE Initial Therapy in MM

Now on the next slide, which is entitled CYCLONE, Initial Therapy in Multiple Myeloma, is an oral presentation by Dr. Mikhail from the Mayo Clinic at the American Society of Hematology, and he did the same thing. He
used carfilzomib, thalidomide and dexamethasone in transplant-eligible patients, but he also added a traditional drug, cyclophosphamide. And so he illustrates that you can combine not only novel agent classes, carfilzomib and thalidomide, but also add in conventional drugs such as cyclophosphamide.

Slide 16: CYCLONE (carfilzomib-cyclophosphamide-thalidomide and dexamethasone) Initial Therapy
And on the next slide entitled CYCLONE (carfilzomib-cyclophosphamide-thalidomide and dexamethasone) Initial Therapy, he further validates what was shown by Dr. Sonneveld and colleagues in Europe, mainly that when you use this combination you get a very high response rate, 96%, with very good partial response in three-quarters. This is very well tolerated, and it is able to prepare people for stem cell collection and subsequent transplantation. So carfilzomib, thalidomide and dexamethasone as initial therapy was highlighted in these two particular presentations by ASH.

Slide 17: Carfilzomib-Lenalidomide and Dexamethasone in Newly Diagnosed MM
But if one moves on now to the next slide, which is entitled Carfilzomib-Lenalidomide and Dexamethasone in Newly Diagnosed Myeloma, this is combining carfilzomib with lenalidomide instead of thalidomide. And what’s shown here on the very first slide and circled in the dotted highlighted area in the left, is the study by Andrzej Jakubowiak et al, who pioneered this regimen and showed that when you put carfilzomib together with lenalidomide and dexamethasone as initial therapy, everybody responds with the extent of response that is truly unprecedented.

So why am I mentioning this? It’s in fact the new carfilzomib-thalidomide-dexamethasone, if you will, it’s carfilzomib-lenalidomide-dexamethasone treatment.

Slide 18: Carfilzomib-Lenalidomide and Dexamethasone in Newly Diagnosed MM
Now on the next particular slide is the result of a presentation by the National Cancer Institute investigators at the American Society of Hematology. They showed that carfilzomib-lenalidomide-dexamethasone induces a very high rate of response very quickly, which can even be a molecular complete response—fewer than one multiple myeloma cell in perhaps a million or ten million normal cells—which can persist over time. And at the bottom of this slide it says PET CT scan improved. Many of you’ll know that PET CT scanning is a very sensitive way of measuring tiny numbers of myeloma cells in the system. And in this study of carfilzomib-lenalidomide-dexamethasone, we’re measuring response not only the traditional way looking at blood proteins or urine proteins or bone marrow aspiration and biopsy, but also now looking for minimal residual disease by molecular techniques or immunofluorescent techniques for fewer than one in a million or one in ten million myeloma cells, as well as using PET CT scanning. So using the new drugs, the second generation proteasome inhibitor carfilzomib together with lenalidomide and dexamethasone, can achieve a response extent greater than ever before, and we can now start to look with more sensitive techniques at how effective we really are at ridding the system entirely of myeloma.

Slide 19: MLN 2238/9708, Oral Chymotryptic Inhibitor
Now if we could move to the next slide, it’s called MLN 2238/9708, Oral Chymotryptic Inhibitor More Potently Blocks Myeloma Cell Growth In Vivo than Bortezomib. On the left hand side, the blue line is human
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multiple myeloma cells growing inside of a mouse. The red line is when the mouse is treated with bortezomib, so the tumor doesn’t grow as rapidly. And the green line is in fact when this mouse is fed an oral proteasome inhibitor, just like bortezomib only oral. Remarkably, many of these mice are cured. And we can remove this human myeloma that’s growing inside of the treated mouse, and on the right hand side the different color stains show that this human myeloma harvested from the mouse treated with this new oral MLN 9708 is dying.

Slide 20: Phase 1/2 Study of MLN 9708, Lenalidomide and Dex
Well, that’s good for the mouse. But what was reported at the American Society of Hematology is on the next slide entitled Phase 1/2 Study of MLN 9708, Lenalidomide and Dex, in Patients with Previously Untreated Myeloma. And just as we’ve already talked about here today with the proteasome inhibitors bortezomib or carfilzomib being combined with thalidomide or lenalidomide, what we’re now showing you here is MLN 9708, an oral proteasome inhibitor, combined with lenalidomide and dexamethasone as initial treatment. Those of you who are patients can appreciate this, but this is a totally oral regimen as the initial treatment for myeloma. It is fantastic, and it’s something we’ve been wanting for a long time.

Slide 21: Phase 1/2 Study of MLN 9708, Lenalidomide and Dex
On the next slide, which is entitled Phase 1/2 Study of MLN 9708, Lenalidomide and Dex in Patients with Previously Untreated Myeloma, are the results of this trial. To summarize it quickly for you, there’s very little in the way of side effects. In particular, peripheral neuropathy has not been a problem as it has been in the past with bortezomib. And excitingly, just as we’ve seen before when you combine proteasome inhibitors and immunomodulatory drugs, the overwhelming majority of patients are responding. Some have already gone forward to have high dose therapy and stem cell transplant. So in my view an all oral regimen is coming to the clinic, very well tolerated, and very exciting indeed.

There is some evidence that this oral proteasome inhibitor, as is true with carfilzomib, also works when bortezomib does not. So these second generation proteasome inhibitors are better tolerated and more potent than the first generation bortezomib.

Slide 22: CALGB 100104 Schema
So let’s move along now to the next slide that’s entitled CALGB 100104 Schema. And what I’d like to just address now is the concept of maintenance after induction treatment. We talked about what’s new for the elderly newly diagnosed patient, and then more recently here we talked about what’s new for the transplant candidate. After initial therapy, what can we do to try to maintain that response?
So this CALGB study shows you that there is a study from the United States where patients who had high dose therapy and transplant in a randomized way then either received placebo or lenalidomide starting at about three months later, in order to see if we could improve the outcome of transplant.

Slide 23: CALGB 100104
And so let’s move along now to the next slide: the red line is those patients who received lenalidomide, and the blue line is those patients who were not taking any maintenance therapy. What this slide shows you is the
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time that myeloma remained inactive, called progression-free survival. That means patients don’t need other therapy and don’t have to endure the side effects and all of the logistical issues that are involved with ongoing therapy, other than oral lenalidomide at 10 milligrams a day which is very well tolerated.

Slide 24: CALGB 100104
And then if one moves to the next slide, the red line shows you that patients who take lenalidomide post-transplant live longer than those patients who don’t. In this United States study, when it became obvious to the independent reviewers that lenalidomide was having a beneficial effect, all of those patients who weren’t randomly assigned to be taking lenalidomide were offered the opportunity to do so. Eighty percent of patients did choose to go on lenalidomide treatment. In spite of this crossover, the red line still remains very superior; what I’m saying is that at the later time points, the majority of patients are on lenalidomide in both of those curves, so very impressive!

Slide 25: IFM 2005-02, Risk Factors for Second Malignancies
Now one concern that many of you have heard about is secondary malignancies and it’s on the next slide entitled IFM 2005-02, Risk Factors for Secondary Malignancies. There has been much publicity about the relative benefit-risk of taking lenalidomide as a maintenance post-transplant. And in fact, there is indeed an increased incidence of secondary malignancies, probably two- to three-fold, in patients taking lenalidomide maintenance.

But if one looks at what are the factors, other than lenalidomide, that might correlate with this increased risk, that’s shown on this particular slide. If you are older than age 55 or a man or had International Stage Disease III, which is advanced disease, those all correlated with an increased risk.

But the reason I show this slide, and I want to highlight for all of us, is that induction with DCEP therapy Cytoxan® VP-16 platinum, multiple DNA-damaging agents, before the transplant, is a very high risk for development of secondary cancers. It probably explains up to two-thirds of the secondary cancers. So the message is not to do away with or avoid lenalidomide maintenance; rather, it’s not to have treatment with so many DNA-damaging agents before the transplant. And in fact, we really don’t do that nowadays. As we’ve already commented, we use combinations of targeted therapies.

Slide 26: Progression-Free Survival and Overall Survival
Now on the next slide, which is called Progression-Free Survival and Overall Survival, this is treatment in the elderly patients, the non-transplant candidates, by Dr. Palumbo. And what this slide shows you, if patients take lenalidomide together with their melphalan-prednisone and then take lenalidomide maintenance (the yellow line on the left), they have a longer period of progression-free survival, time during which the myeloma is inactive. So just like in the transplant patients, so it’s true here in the elderly, lenalidomide maintenance is helping.

On the next slide the same question of the secondary cancers is looked at very carefully.
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Slide 27: Second Primary Malignancies
This slide is entitled Second Primary Malignancies, All Patients, and I think it’s one of the most important concepts. If you look at the green lines here on the left hand side, it’s melphalan-prednisone, lenalidomide, plus lenalidomide maintenance; and in the center, melphalan-prednisone-lenalidomide; and on the right, melphalan-prednisone alone. In each case the green line is the likelihood of myeloma progressing or dying of myeloma, and the white and the pink lines are the chances of getting a secondary blood or non-blood cancer.

And what you can see is the benefit-risk ratio is far in favor of taking lenalidomide maintenance. I personally have somebody who’s in his thirteenth year now of taking lenalidomide maintenance and remains progression-free. So this is an overwhelming endorsement of using lenalidomide as maintenance, whether you’re a transplant candidate or not.

Slide 28: GEM05MENOS65
Now at the American Society of Hematology there was also a randomized trial using bortezomib after a transplant. So on the next slide entitled GEM05MENOS65, the only point I want to make here is that these patients all had autologous stem cell transplants. They were then randomized after that to get interferon, thalidomide, or thalidomide and bortezomib as a maintenance, to prolong the response.

Slide 29: Conclusions
And if one moves to the next slide entitled Conclusions, the point here is that the patients who took bortezomib and thalidomide actually had a longer progression-free period of time during which the myeloma was inactive. So the overwhelming message is that novel agents can be used initially, and should also be used as maintenance.

Slide 30: Pomalidomide in Myeloma
Well, what about if myeloma comes back? The American Society of Hematology gave us some hope in that context. The next slide is entitled Pomalidomide in Myeloma. It’s an old slide really because pomalidomide in the laboratory was studied almost 15 years ago now, but this slide shows that pomalidomide not only targets the myeloma cells directly, but doesn’t allow them to bind to the bone marrow, as well as blocks factors in the bone marrow that help the tumor grow and survive and resist drug. And in the lower right hand corner, pomalidomide, lenalidomide and thalidomide turns on your own immune system: natural killer cells, T-lymphocytes, and the hybrid of those two, the natural killer T cell. All of these cells are the good guys that, if you will, are turned on by pomalidomide to kill myeloma in patients who are treated.

Slide 31: Pomalidomide with Low-Dose Dexamethasone
So at the American Society of Hematology, in the next slide entitled Pomalidomide with Low-Dose Dexamethasone for Relapsed and Refractory Myeloma, Sundar Jagannath from New York City, Mount Sinai Medical Center, presented the results that will lead to the accelerated approval of pomalidomide within the next week or two. What he showed quite plainly is the second bullet point on this slide, namely that pomalidomide, this new immunomodulatory drug stronger than lenalidomide, together with low dose
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dexamethasone achieved 34% response. A third of patients responded, even when myeloma was resistant to everything else. These responses lasted 8.8 months and patients lived years longer. That is the database upon which the accelerated approval will be based, and as I just shared, it’s coming soon.

Slide 32: Pomalidomide Plus Low-Dose Dexamethasone in Relapsed Myeloma
Now on the next slide there is also, entitled Pomalidomide Plus Low-Dose Dexamethasone in Relapsed Myeloma, there is the experience summarized from the Mayo Clinic, which confirms this wonderful activity of pomalidomide. Martha Lacy and her colleagues showed high response rates, even in patients whose myeloma was resistant to bortezomib and lenalidomide. They showed that it was very well tolerated. And you could predict who would respond better or not by the number of prior therapies and the kinds of prior therapies. So prior exposure to lenalidomide, for example, did predict for a lower response. Nonetheless pomalidomide is going to be offering us new hope in myeloma.

Slide 33: A Phase III Clinical Trial of Pomalidomide with Low-Dose Dex vs. High Dose Dex
Now on the next slide, A Phase III Clinical Trial of Pomalidomide with Low-Dose Dex Versus High-Dose Dexamethasone in Relapsed-Refractory Myeloma, is a study that was presented by Dr. Dimopoulos from Greece. It’s a late-breaking abstract, so this was thought to be very newsworthy indeed. This non-U.S., primarily European study, utilized the same pomalidomide and low dose dexamethasone regimen that we think will be approved in the U.S., versus high dose dexamethasone in a randomized trial in order to see which was superior in terms of efficacy and tolerability.

In spite of the fact that patients had myeloma refractory to both lenalidomide and bortezomib, pomalidomide-low dose dex was active and well tolerated. This Phase III study will be the basis for pomalidomide getting approved in Europe.

Slide 34: MM-005
Now what can we do with pomalidomide now that we know with low dose dex it works well? On the next slide entitled MM-005, a Phase I Trial of Pomalidomide-Bortezomib and Low-Dose Dexamethasone, my colleague Paul Richardson carried out a study combining pomalidomide with bortezomib. Remember the immunomodulatory drug together with the proteasome inhibitor class of drugs is very, very active, regardless of which proteasome inhibitor and regardless of which immunomodulatory drug. Here he took the new agent, pomalidomide and showed that you could give the full dose pomalidomide 4 milligrams, with the full dose of bortezomib at 1.3 milligram per meter squared. Even in patients with far advanced myeloma, three-quarters of patients responded, which is very impressive activity. And in the U.S. there’s an ongoing trial now of bortezomib, pomalidomide, dexamethasone, versus bortezomib, dexamethasone, that will extend the approval of this novel agent pomalidomide to full approval in the United States.

Slide 35: Carfilzomib in Relapsed/Refractory MM
There’s a slide entitled Carfilzomib in Relapsed/Refractory Myeloma. And what you can see in the center of this slide is the data upon which carfilzomib was approved in relapsed-refractory myeloma. Namely, at a dose of 20 to 27 milligrams per meter squared, it achieved an overall response rate of 24%. At the bottom of this
DR. KENNETH ANDERSON:
slide there’s preliminary data suggesting that if you go to a higher dose of carfilzomib in patients with advanced myeloma, as high as 56 milligrams per meter squared, that the response rate might go as high as 60%.

Slide 36: Phase II Study of Infusional Carfilzomib in Patients with Relapsed or Refractory MM
So on the next slide entitled Phase II Study of Infusional Carfilzomib in Patients with Relapsed or Refractory Myeloma, Dr. Lendvai and colleagues tried to increase the dose of carfilzomib with an infusion strategy, to try to see if you could get higher response rates.

Although one could get higher response rates, there were more frequent cardiac and pulmonary toxicities, high blood pressure, and congestive heart failure. So it tells you that we need to be careful as we combine these more potent agents. With carfilzomib, the very potent proteasome inhibitor, it may be that there’s a dose-response relationship, but we have to be very careful, since there may also be a dose-side effect relationship as well.

Slide 37: Carfilzomib Pomalidomide Dexamethasone (Car-Pom-d) in Relapsed/Refractory MM
And then on the next slide, carfilzomib was combined with pomalidomide. So this slide is entitled Carfilzomib-Pomalidomide-Dexamethasone in Relapsed/Refractory Myeloma. Carfilzomib is already approved, pomalidomide and dexamethasone is soon to be approved. And already they are being combined in clinical trials. This slide shows in the boxed area that if you combine these two potent agents at their regular doses of 4 milligrams of pomalidomide and 27 milligrams of carfilzomib, high response rates can be achieved in far advanced myeloma. So either agent is active alone, but together they’re even more active. Again here the caution is that they’re both so potent that you probably can’t escalate very far when you combine them. Nonetheless, you do get higher response rates.

Slide 38: MAb-Based Therapeutic Targeting of Myeloma
So let’s move on now. We’ve talked about using new agents as initial therapy. We’ve talked about maintenance treatment and then the therapy for relapsed-refractory myeloma. I want to mention examples of monoclonal antibody-based therapeutic targeting of myeloma, as on the next slide. The myeloma cell can be targeted specifically and attacked by antibodies in three different ways. The antibodies can stimulate effector cells to kill myeloma (left). The antibodies can kill myeloma directly (center). Or the antibodies can blow the fuse on circuits that the myeloma cell needs to grow or survive or resist drugs (right).

Slide 39: A Phase 2 Study of Elotuzumab
So on the next slide entitled A Phase 2 Study of Elotuzumab with Lenalidomide and Low Dose Dexamethasone in Relapsed-Refractory Myeloma, elotuzumab has been combined with lenalidomide and low dose dexamethasone in relapsed multiple myeloma. Excitingly, lenalidomide, the oral agent, activates the antibody to work better. There’s more antibody-dependent cytotoxicity or killing of myeloma when you combine the antibody with lenalidomide. Moreover elotuzumab, an antibody targeting myeloma, together with lenalidomide and dexamethasone, not only achieves higher response rates, but also markedly prolongs progression-free survival to 29.7 months, as shown on this slide. That means that patients are having and enjoying a long response.
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It is predicted that lenalidomide and dexamethasone treatment without antibody would lead to progression-free survival of only about 11 months in this context. So by adding the antibody we have literally more than doubled the duration of the responses.

Slide 40: Daratumumab
And then on the next slide, daratumumab is a second antibody that targets another fingerprint protein on myeloma called CD38. Just like the elotuzumab, it can act by stimulating effector cells to kill myeloma or directly stimulate the death of myeloma. It can also blow the fuse on circuits that are needed by the myeloma cells to survive.

Slide 41: Phase I/II Study of Daratumumab
On the next slide, at the American Society of Hematology, investigators from Europe, together with Boston, presented early studies with this antibody called daratumumab used by itself. In this case no lenalidomide added. And what you can see is that half the patients treated with advanced myeloma had a benefit, and that it was well tolerated. And the potential advantage of the antibodies that I’ve just mentioned, elotuzumab and daratumumab, is they may work even in the context of adverse cytogenetics, such as 17p deletion. So excitingly this new class of monoclonal antibodies, elotuzumab and daratumumab, is coming to the clinic relatively soon.

Slide 42: Factors Impacting QOL
Now I want to finish up with just a few closing thoughts on quality of life. I mentioned at the outset that we are able to have new unprecedented outcomes together when we use new drugs early, consolidating response, and as maintenance. We have new hope for treating relapsed myeloma with the second generation agents, either separately or alone. So patients are living longer, but can we improve the quality of life?

A few thoughts about neuropathy, low blood counts, blood clots, fatigue, shingles and bone disease, just to finish up.

Slide 43: Management of Peripheral Neuropathy
Peripheral neuropathy, on the next slide entitled Management of Peripheral Neuropathy, is very, very important. Those of you who are patients and we who are caregivers carefully watch for this and promptly act by reducing the dose or changing the frequency. We do use supplements to try to prevent or prophylax against neuropathy. Once it develops, we have in fact medications as listed here, including antidepressants, pain, and neurologic agents, that can be used. It is much better to avoid this complication, so be on the lookout for early signs of peripheral neuropathy and try to intervene early to prevent it from becoming worse.

Slide 44: Prophylaxis and Treatment
Now the next slide is entitled Prophylaxis and Treatment. And again the detail here is not important, but this list was developed by our nursing staff and includes vitamins, supplements, and strategies such as cocoa.
DR. KENNETH ANDERSON:

butter or menthol-based creams, that can be used not only to treat neuropathy, but also to prevent neuropathy from developing. So I would encourage you all to visit the web, look at these different prophylactic measures, and try to employ them to prevent the development of neuropathy.

Slide 45: Drug-Induced Cytopenia

The next slide is entitled Drug-Induced Cytopenia or low blood counts. Shown at the top of this slide is the fact that some of our novel agents, such as the proteasome inhibitors and IMiDs, can lower blood counts. And when we combine targeted therapies with each other or with conventional therapies, we together need to be looking out for low blood counts.

It matters what’s causing the low blood counts in terms of how we manage it. If it’s disease, we have to treat the disease and deal with the low blood counts, with growth factors for transfusion, for example. If low counts are related to a treatment—lenalidomide for example—we might reduce the dose. We need to monitor closely and define the cause of those cytopenias or low blood counts and may need to treat myeloma in spite of low blood counts.

Slide 46: Risk Assessment Model for VTE Management in MM

Now the next slide is the Risk Assessment Model for Venous Thrombosis Embolism Management in Myeloma Patients Treated with Thalidomide or Lenalidomide. Again, this slide is probably more useful for the web, if anybody wants to visit it. But on the right hand side the only point I want to make here is that one needs to take aspirin, 81 milligrams a day with these immunomodulatory drugs. If there’s a history of clotting or other factors that might put patients at risk for clots, then more aggressive prophylaxis with heparin or Coumadin might be necessary. However, the standard is low dose aspirin for patients on thalidomide, lenalidomide and on pomalidomide, when it’s approved.

Slide 47: Fatigue

Now the next slide is fatigue, which I might add is shared by the caregivers and patients alike. I put this slide in because fatigue can be multifactorial. So it’s important for you and your caregiver to define the causes if you can. Certainly it’s disease related in some circumstances. It can also be related to anemia or low red blood cell count. It can be related to drugs directly, or it can be related to the side effects of drugs, ie hypoadrenalism or low levels of thyroid hormone, etc. One needs to define if there’s a medical cause that can be treated by changing medicines or reducing the dose of a drug or supplementing thyroid, for example.

At the bottom of this slide, there is the important need to keep oneself with diet, with nutrition, with physical conditioning, as much as you can, in the best shape possible. So avoiding fatigue is what I’m mentioning. So that we won’t have to interfere with treatment and so that it won’t interfere with your daily life.

Slide 48: Herpes Zoster Prophylaxis With Bortezomib Treatment

The next slide is another comment on herpes zoster prophylaxis with bortezomib treatment. Those of you who have used or are being treated with bortezomib know that one needs to take prophylaxis against shingles or herpes zoster if you’re on a proteasome inhibitor. If you do take acyclovir or some other prophylactic, you
DR. KENNETH ANDERSON:
can avoid this complication. I mention it because it’s routine nowadays, but it needs to be extended to the
new proteasome inhibitors that I mentioned here today, carfilzomib and MLN 9708. As they come and
already are in the clinic, you will need to use some prophylaxis against shingles in patients when treated with
these drugs as well.

Slide 49: ASCO Clinical Practice Guidelines for Bone Disease
And my final slide is entitled ASCO Clinical Practice Guidelines for Bone Disease. You all know as patients that
bone disease occurs in 80% of patients. It is the most evil complication of our disease, limiting performance
status and causing pain. And together we use aminobisphosphonates, as shown on this slide. Zoledronic acid
or zoledronate, are used for an average of two years in patients who have active myeloma and then can be
used at lesser intervals, perhaps every three months thereafter. One does need to be careful of complications
such as osteonecrosis of the jaw or kidney dysfunction, but the overwhelming benefit is for two years of
therapy, and then in patients who are responding decreasing the frequency of treatment. Novel bone
therapies are coming along here as well, so you can anticipate in the future that there’ll be alternatives to
treat bone complications as well.

Slide 50: Summary of ASH 2012
So my last slide is a Summary of ASH 2012. It’s one of great hope. Together we’ve had remarkable progress
over the last decade, but the best is yet to come. Why? Because we’re learning to use the novel agents we
already have better, as initial, consolidation, and maintenance therapy. Fortunately, we have stronger second
generation IMiD pomalidomide, as well as second generation proteasome inhibitors carfilzomib and MLN
9708. I mentioned how we can use them in combination, and that they’re even better than when used alone.

I mentioned two examples of monoclonal antibodies, elotuzumab and daratumumab, and one or both of
them are surely going to be coming to the clinic.

And importantly, with all of this improvement in outcome, we need quality of life, so I updated treatment of
side effects.

My closing comment is this. All of this progress is possible only because of those of you who are patients on
the phone who have been willing as our heroes and inspiration to participate in the clinical trials. So we could
not be more grateful to you. It really is a labor of love for all of us, and in fact the best is yet to come.

My final thank you again is to the LLS because with all of this progress, it’s only meaningful if we can have
sessions like this today, where in real time those of you who are caregivers and those of you who are patients
alike can appreciate the progress, and we can make sure that these advances get to the patients who so
desperately need them.

Thank you ever so much.
LAUREN BERGER:
Thank you so much, Dr. Anderson, for an informative presentation with so much new information. It is now time for the question and answer portion. We’ll take the first question from the web audience and this question is from Dan. “Does the level of the M-spike protein being not observable indicate that myeloma is in remission?”

DR. KENNETH ANDERSON:
That is a very good question from Dan. I think that it is one of the parameters that we follow in patients whose myeloma actually is characterized by production of an M-protein. But it is only one of the features. As we assess the extent or stage of myeloma or as we assess the impact of treatments that we talked about here today, we certainly follow the M-protein, which stands for myeloma or monoclonal protein. If it’s present, we can measure it as an IgG or an IgA, and we can measure it also by the Kappa Lambda free light chain ratio. But we also use clinical features. We look at bone disease, and we look at blood counts. And there are some patients whose myeloma does not make significant amounts of M-protein—so called non-secretory myeloma. In those cases we have to look at the bone marrow aspiration or biopsy, or more recently we’re using the PET CT scan to monitor disease.

So the answer plainly is yes, we use the M-protein as part of our analysis, but it’s not the total story, it’s only part of the picture.

LAUREN BERGER:
Thanks for your question, Dan. We’ll take the next question from the telephone audience, please.

OPERATOR:
The next question comes from Michele from West Virginia. Please state your question.

MICHELE:
Hi, Dr. Anderson. I wanted to ask whether you recommend maintenance therapy post-stem cell transplant all the time or particularly even if there’s a complete response.

DR. KENNETH ANDERSON:
That’s a super question. And the issue is, it’s still in evolution. But as I shared with you today, there is a large study in the United States that showed that lenalidomide did improve outcome. There’s a similar large trial in France that showed the same thing. And it showed benefit, even in patients who had a complete response. So I think the answer is yes, that we should use lenalidomide maintenance, even if one gets a complete response, because there was a prolongation of benefit in that setting.

Now I want to mention something quickly here. Lenalidomide is the maintenance I think that is established as of 2013, but there are studies of maintenance therapy with the oral proteasome inhibitor MLN 9708, because it’s oral and well tolerated, and you only have to take it once a week. So please be aware that some patients
DR. KENNETH ANDERSON:
may be taking other maintenance therapies. You can even envision in high risk myeloma perhaps some day taking lenalidomide and MLN 9708 together. But at present, the lenalidomide would in my view be considered a standard.

LAUREN BERGER:
Thank you for your question. We’ll take the next question from the web audience and this question comes from Marcie. “Is it beneficial to reinstate lenalidomide maintenance therapy that was started after transplant and was discontinued for fear of getting a secondary cancer? I was on lenalidomide for over a year and have been off the drug for six months or so.”

DR. KENNETH ANDERSON:
That’s a super question. And obviously we don’t have any studies to point to in order to answer that on a data-driven basis. I will hasten to add, however, that I think we know from historical data that if one doesn’t use some form of maintenance, myeloma usually does return after an autologous transplant. So it’s not a matter of if it will return, it’s a matter of when.

So I think in the context of an oral agent like lenalidomide, which really doesn’t have many side effects at low level of 10 milligrams orally, I would try to use it.

You know, the closest answer I can give you data-wise is from that big large trial in the United States, because people either took lenalidomide or not after transplant, and those who weren’t randomly assigned to take lenalidomide, once the advantage became obvious, were offered the opportunity to do so. So some of them started lenalidomide a year or two years after their transplant, so it’s a little bit like this question, where there’s an interval where lenalidomide wasn’t used. But my point would be—I think if all other considerations allow, that is blood counts, etc., I think I would do that.

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

OPERATOR:
The next question comes from William in Tennessee. Your line is now open.

WILLIAM:
I was wondering about the low counts of WBC, the RBC, the HTB, the HCT. They’re not addressing that they’re low. They’re just saying they’ll be fine.

DR. KENNETH ANDERSON:
Right, that’s a very nice question. If you have the ability to peek at the slides on the web after this, where I had the slide called cytopenias, that’s medical jargon for what you just asked about. It’s low blood counts. And so the low white blood cell count is leukopenia, the white cells fighting infections, and the low HCT is the low hematocrit or low red blood cell count. Those red cells carry oxygen, so they could be responsible for fatigue.
DR. KENNETH ANDERSON:
if you don’t have enough red cell mass. And then the PLTS, platelets, help the blood clot and prevent bleeding. And when they’re low, it’s called thrombocytopenia or low platelets.

What I tried to stress real quickly is it could be disease-related, too much myeloma; it could be drug-related, old drugs or even the novel targeted therapies could be causing low blood counts; or it could be other reasons. And so it really does matter. You and your provider do need to search for the cause of the low blood counts. If it’s myeloma, it might mean more heavy or switching treatment. If it’s related to a medicine, it might be switching or reducing the dose of the medicine. But you can’t really give a specific answer except to say to look carefully for the cause of the low blood counts together, and then do the appropriate intervention.

LAUREN BERGER:
Thank you for your question, William. We’ll take the next question from the web audience and this one is from Paula. “How do these treatments change when the patient also has primary amyloidosis?”

DR. KENNETH ANDERSON:
That is a super question from Paula. Primary amyloidosis, for everybody’s benefit, is the deposition or the accumulation, if you will, of a small protein fibril called amyloid. And it accumulates throughout the body, not only in the bone marrow, but much more commonly and tragically it accumulates in the organs, the heart or the liver or the kidneys, etc., sometimes the lungs. And it is a very sinister illness. And not very long ago we were not able to really effectively treat primary amyloidosis very well.

But what’s so exciting is, and again that would be the subject for another day to be honest, is that the lenalidomide and the bortezomib, when utilized either separately or together in primary amyloidosis, have really achieved high rates of response. Now in amyloidosis the way we measure response is to see whether the organs function better—does the heart contract better, does the liver or kidney work better. And with conventional drugs, that didn’t happen very often. But with the novel drugs alone or particularly together, so RVD, lenalidomide-bortezomib-dexamethasone, can achieve remarkable response rates, even in the context of primary amyloidosis. So please use novel targeted agents in that setting, too.

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

OPERATOR:
The next question comes from Barney in Pennsylvania. Your line is now open.

BARNEY:
Dr. Anderson, how are you? I have a little different story than most. After my second coma from bacterial meningitis, it was diagnosed that I needed Gammagard and I take an infusion every four weeks. And as you know, Gammagard is made from human plasma cells. And soon thereafter I was diagnosed with myeloma and my blood counts for the past seven years have been level. And I’m wondering if you’ve had any clinical studies using positive human plasma cells.
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DR. KENNETH ANDERSON:
What I would say to you is that, in the context of multiple myeloma, we sometimes use gammaglobulin treatment. And the times we use it are in patients who have repeated, life-threatening infections. I don’t want to be too specific here about your individual case, but meningitis infection around your brain is a life-threatening infection. So the fact that that occurred, and if it occurred more than once especially, is an absolute indication for using antibody or immunoglobulin. And as you correctly said, it’s a transfusion, if you will, of antibodies that fight infection. They have been harvested and collected from multiple individuals and put in a transfusion and given to you to protect you in a passive way from any more life-threatening infections.

In multiple myeloma, where the antibody level is low and ability to fight infection is compromised, we do use the immunoglobulin, but we only use it in the setting where you have repeated life-threatening infections. It does seem to me, from what you’ve said, that you would be appropriately treated with that agent. Now whether or not it helps myeloma or not I think is debatable, but it is unquestionable that it would help you in terms in decreasing the frequency and the severity of future infections.

LAUREN BERGER:
Thank you for your question, Barney. We’ll take the next question from the web audience and this question is from Deborah. And she asks, “Have you seen central nervous system neuropathy with bortezomib? And if so, what remedies are effective?”

DR. KENNETH ANDERSON:
This is a very, very good question, too, from Deborah. I think that classically the bortezomib neuropathy is thought to be a peripheral neuropathy, characterized by numbness and tingling in your fingers and toes. It’s more sensory than motor weakness and inability to walk because of loss of strength. Classically the neuropathy from bortezomib does resolve when one discontinues the drug. It takes about 90 to 100 days for that to happen in the majority of patients.

In terms of central nervous system neuropathy, we really don’t see that very commonly in terms of confusion or other manifestations that might suggest central nervous system issues. We can’t say that it doesn’t happen, but what I would say is that one needs to look very carefully for other causes including infection, myeloma or other reasons why the central nervous system might be impacted, besides the drug, before concluding that it’s related. It would be very unusual for that to be the case.

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

OPERATOR:
The next question comes from Joanne in Rhode Island. Please state your question.

JOANNE:
Hi. My question is, I take steroid meds and spinal injections for my back and I was wondering if they affect the bone marrow results and blood work results for the M-protein.
DR. KENNETH ANDERSON:
Okay, that’s a very good question. The steroid injections—I think it sounds like they are being given locally for symptomatic relief. I think that those would be given around a particular spot in your backbone or spine and should be working primarily by decreasing inflammatory cells or inflammatory reactions around an area. Or if there were myeloma there, they could in fact work against the plasmacytoma I suppose. But the answer is that steroids are active in multiple myeloma. Traditionally we give them either orally or by vein. What I would be not sure of is how much of that steroid that you’re actually getting locally injected into the back actually gets absorbed or is effective beyond the local area where it’s being given to control pain. So I think it could affect the protein, I guess, but it wouldn’t be a major effect, and it doesn’t mean that you wouldn’t need treatment systemically for multiple myeloma in addition to those injections.

LAUREN BERGER:
Thank you for your question, Joanne. We’ll take the next question from the web audience please and this one is from Christina. And Christina asks, “If thalidomide was not tolerated, what are the chances of pomalidomide being tolerated?”

DR. KENNETH ANDERSON:
That’s a super question and it just shows how really current and up-to-date the patients are. It’s just wonderful. I will share with you a big surprise. Thalidomide, some of you will remember who have been treated with it, has side effects of sleepiness and constipation and neuropathy. And pomalidomide looks very similar in terms of its structure as a medicine. So those of us who are patients and caregivers alike, were worried, if you will, or wanted to be cognizant of the fact that neuropathy might be a complication. But I can happily tell you, and some of you undoubtedly have had pomalidomide here on the phone, that pomalidomide doesn’t cause any of those things. It doesn’t cause sleepiness, it doesn’t cause constipation, and excitingly unlike thalidomide, the neuropathy has been minimal. So we have a more potent agent that is better tolerated. That’s the reason for all the excitement.

LAUREN BERGER:
Thanks for your question, Christina. We’ll take the next question from the telephone audience, please.

OPERATOR:
The next question comes from Richard in New Jersey. Your line is now open.

RICHARD:
Good afternoon, Dr. Anderson. I’d just like to congratulate you as being a crusader and also caregiver for all of us multiple myeloma patients. I’m in the early stages of going into a clinical trial for MLN 9708, which has probably a name to it, but I don’t know it. I believe it begins with an LX and ends with OMIB.

But anyway, my questions are, I was diagnosed four years ago and went through the Revlimid-dex treatment and then also autologous stem cell transplant, which lasted about two years. And then I relapsed a year and four months ago. During that course, after transplant, I was not on any maintenance. And now they find that
RICHARD:
my M-spike is at 2.0, so they decided, I have a choice of going into a clinical trial at the John Theurer Cancer Center, which is a blind side study, where half the patients will get the MLN 9708 and the other ones will get a placebo. But I also have a choice of just getting normal therapy and not going into it, but I encourage everyone that's in the listening audience to go on a clinical trial if things are not going that good, because it's going to benefit not only people now, but people in future generations. And that’s basically my comment. Thank you.

DR. KENNETH ANDERSON:
Thank you very much for the kind words. I think that the heroes and honestly the inspiration for everything we do every day is you and all the other patients here on the phone and around the world. And as I said in my closing comments, if it weren’t for your willingness to go on a clinical trial, we would not be making any progress. The wonderful support and the awareness and education that LLS is supplying in making sure that all of you know this information, like conferences today, are great. Honestly, we’re reporting progress today because of the ability of patients to go on clinical trials. So I would very much encourage you to do that.

I think that MLN 9708 has very big strengths in the sense that it’s well tolerated. You only have to take one tablet once or twice a week. And as I said in my earlier comments, it does work in at least some patients whose myeloma is not responding literally to anything else.

So I think to go on the trial, Richard, is very reasonable. And then there are other options, whether they be conventional or other new drugs awaiting you—that’s our mutual goal—to be there if and when you need us.

LAUREN BERGER:
Thank you for your comments, Richard. We wish you the best. And if anyone wants additional information on clinical trials or how to find one, please call an LLS Information Specialist at 800-955-4572.

We’ll take the next question from the web audience and Enid asks, “Do you have any recommendations for nerve pain following shingles and also recommendations for preventing shingles in patients with myeloma?”

DR. KENNETH ANDERSON:
That’s a very good question and I tried to kind of anticipate it. And so, Enid, what I would kindly ask, too, is if you get a chance to peek at the slides or look at the web later, in terms of both the neurologic pain and also the herpes zoster or shingles, we have a little discussion of both of those. But suffice it to say, in terms of herpes zoster, patients with myeloma are more likely to get shingles just by virtue of the myeloma. That’s not usually an indication to take medicines to prevent it, as the risk isn’t that high. But if you are taking proteasome inhibitors, whether that be bortezomib or whether you’re starting on some of these new agents like carfilzomib or MLN 9708, you will need to take some form of prophylaxis. And usually the starting prophylaxis is acyclovir.

Now in terms of pain medicine for neuropathy, I also mentioned that a little bit, and I stress it’s really important, if we can, to prevent rather than try to treat neuropathy. And we have some strategies included for that. But if one does actually develop painful neuropathy, that is likely going to impact on the ability to take the medicine, or at least take it at the same dose and schedule. So some change is probably likely.
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DR. KENNETH ANDERSON:
And then yes, we have Neurontin® (gabapentin), Lyrica® and other medicines that can be used as, if you will, symptomatic treatment. For example, in bortezomib-related neuropathy, changing the dose or schedule or discontinuing it in the vast majority of patients does result in resolution of the neuropathy.

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

OPERATOR:
The next question comes from Richard in California. Your line is now open.

RICHARD:
I have been diagnosed with multiple myeloma, but I’m the smoldering stage. And I’m just wondering, is there any new study about when treatment should begin, at what point? If that makes any sense.

DR. KENNETH ANDERSON:
Well, Richard, that’s a super question. And just so everybody is on the same wavelength here, smoldering myeloma is characterized by lesser amounts of myeloma, lesser number of plasma cells in the bone marrow, lower amounts of monoclonal proteins, and no other complications such as anemia or low red cell count, bone disease, kidney dysfunction, or high blood calcium. In other words, there is no real urgent need to treat.

Now in patients who have smoldering myeloma, we can tell who’s more likely to need treatment in the near term than who isn’t, 1. by virtue of the kind of M-protein they have. If it’s a non-IgG, it’s more likely to progress; 2. in terms of the amount of the protein that is monoclonal protein; and 3. in terms of another measure called the Kappa Lambda ratio in the blood being high. Therefore we can predict who among the smoldering patients is more likely to get active myeloma.

But to get right to Richard’s point, we would never treat smoldering myeloma in the past, and right now the standard of care is not to do so. But since we have novel agents that are pretty well tolerated and very active in patients who need treatment, who have active myeloma, now there are clinical trials ongoing of oral lenalidomide or vaccines to try to prevent smoldering myeloma from becoming active. Trials also include antibodies, such as the elotuzumab antibody that I mentioned. So novel treatments, immune treatments and other strategies are now being tested in many clinical trials in smoldering. The thought is, if these agents work even when we have very active advanced disease, wouldn’t they work much better very early? And we’re even thinking about together here about whether it possible to prevent the development of active myeloma. That obviously would be wonderful.

So standard of care is no treatment, but if you have options for clinical trials you might consider them.

LAUREN BERGER:
Thank you for your question, Richard. We’ll take the next question from the web audience and this one is from Wayne and Wayne asks, “Could you comment on T cell and T cell receptor therapy in myeloma? For example, Carl June at Penn?”
DR. KENNETH ANDERSON:
That’s a super question and I will just mention that there’s great excitement for so-called immune treatments. I couldn’t, obviously, talk about everything here today, but in the questions I think we’re extending the information, which is fantastic.

The immune treatments come in various kinds, but the antibodies I mentioned, elotuzumab and daratumumab, they are immune treatments. Vaccines are immune treatments and we have several of those being tested in clinical trials. But as you just said, so are the T cell therapies. And just for everybody’s benefit, T cells are immune cells that are circulating in each of us, and it is thought that in multiple myeloma that one of the reasons myeloma can grow and survive as it does is because your own God-given endogenous immune system, in particular your T cells, are not effective at recognizing and killing the myeloma as they should be, just as they reject infections or other noxious stimuli.

So Carl June and his colleagues have actually genetically programmed patients’ own T cells to recognize their own leukemias and myelomas, and then transfuse back to the patient, him- or herself, their own T cells that have been taken from them and educated or programmed genetically to recognize myeloma. They are then transfused back to the patients and achieving quite remarkable responses.

Now the excitement here is that the immune system that we all have is in fact very, very potent. If you could restore immunity against multiple myeloma, it would be more effective than, honestly, any other treatment. So the excitement here is potentially taking your own immune system and waking it up to recognize the myeloma, which it isn’t doing in a selective way. And so yes, we’re very excited about that. Dr. June at Penn is doing that. There is additional work at the National Cancer Institute. And at one or two other sites. But we think it is very promising indeed.

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

OPERATOR:
The next question comes from Richard in Texas. Your line is now open.

RICHARD:
Yes, Dr. Anderson, you mentioned earlier that myeloma usually returns after an autologous stem cell transplant. However, the transplants do help. Is there a limit to the number of transplants that a patient can have?

DR. KENNETH ANDERSON:
So that’s a very good question, Richard, and I for sure want to be clear that the transplants have helped remarkably in myeloma. There have been many randomized trials comparing high dose therapy and transplant versus standard treatment, and high dose therapy has clearly changed things for the better. And in particular when you use new medicines, as I discussed with combinations of targeted agents before the transplant, right after the transplant to increase the response and then as maintenance, there’s no question that transplant has markedly improved things. And I think it’s fair to say that patients are often living a decade or more, and we don’t know how long that’s going to be with maintenance in the context of transplant.
DR. KENNETH ANDERSON:
It’s so exciting, in fact, that we now have trials that are looking at whether you can just use combinations of novel drugs and not do the transplant. So for example, lenalidomide-bortezomib-dexamethasone with or without a transplant is being tested now in an international trial.

But suffice it to say transplant has been very useful and remains the standard of care. Now more than one is a very exciting issue, too. What I would say is that there are studies now showing that patients can benefit from a second transplant, but it’s primarily the patients who have had a very good response to the first. In other words, if you enjoyed years of time, more than two years, for example, of benefit during which time the myeloma has not been active and you have not required therapy, then perhaps consideration of a repeat transplant would be useful. Usually the benefit that one achieves in that setting is about half as much as you achieve with the initial transplant.

But I would hasten to add, and I hope you’ve heard, exciting discussion here today about all of the other options. So although transplant remains an option, you’ve already heard about some very potent new targeted agents that are working in patients who have had one or even two transplants. So I think you need to discuss this carefully with your caregiver, and see where the second transplant ranks in the benefit-risk assessment at a given point for a given person.

LAUREN BERGER:
Thank you for your question, Richard. We’ll take the next question from the web audience. Edith asks, “What is your opinion on the use of curcumin for smoldering myeloma?”

DR. KENNETH ANDERSON:
Yeah, so this a very, very good question. So curcumin I think is known to all of us, very common in Indian cuisine, for example. And it has been popularized as something to potentially use in myeloma or even in smoldering myeloma because at very high doses it inhibits something called NF-kappaB, a switch that turns on one of the circuits the myeloma cell uses to survive and resist drugs. So the idea is that you could use curcumin to, if you will, blow the fuse on that circuit and have benefit.

Now the issue is not whether inhibiting NF-kappaB is a good idea. The issue is whether or not one can take curcumin and get doses and levels high enough to be able to inhibit that circuit in a meaningful way. So I think using it earlier, like in smoldering myeloma, does have appeal. I would ask and hope that if we do such maneuvers in smoldering myeloma, if at all possible, let’s try to do it in the context of a clinical trial, where the doses and schedule would be such that you might expect to inhibit this NF-kappaB and where results would be collated, so we could all learn together whether that is useful or not.

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

OPERATOR:
The next question comes from Elizabeth in Michigan. Your line is now open.
ELIZABETH:
Hi, Dr. Anderson. I have a question. I’m taking Revlimid, 25 milligrams, as maintenance. I had taken the Velcade and I got a good response, had extramedullary plasmacytoma that they haven’t found, and so I’m staying on just Revlimid 25 milligrams. And I was wondering, at some point would they be able to decrease the dose, do you think, that that’s possible? Or is it safe to stay on 25 milligrams of Revlimid indefinitely?

DR. KENNETH ANDERSON:
This is a super question. I can’t be too specific because I don’t know all the details, but I think what I would share that you mentioned a couple of interesting and important points. Extramedullary plasmacytomas are in fact often refractory to treatment, so we do often use proteasome inhibitors. You had bortezomib and immunomodulatory drugs alone or together. And it may be that using the higher dose of lenalidomide is more warranted in that setting. I don’t know if you’re taking dexamethasone along with it, but usually when we do lenalidomide at 25 milligrams and dexamethasone at 40 milligrams orally once a week, that’s really a treatment dose—not really considered a maintenance. So it’d be considered continuous treatment, if you will.

The answer is, it can be very well tolerated, and I think, again, discuss with your caregiver the reasons behind staying at that high dose, and whether it is warranted to try reducing it down to a lower dose and seeing if that maintenance schedule could be effective.

LAUREN BERGER:
Thank you for your question, Elizabeth. We’ll take the next question from the web and this one is from Tracy and Tracy asks, “Can you speak to the benefits of utilizing complementary therapies such as acupuncture with regard to pain?”

DR. KENNETH ANDERSON:
This is a super question and very, very relevant in today’s world, especially. There are studies that have shown that at least 80% of patients are taking some kind of therapy. It used to be called alternative or complementary therapy, but today it’s most commonly called integrative therapy. And that term is probably the most relevant. The answer is an overwhelming yes, we do support it, believe in it, and think that integrative therapy makes a huge difference. But what needs to be done, as the term implies, is that it needs to be integrated with other therapies for your multiple myeloma. So it’s not either-or, it’s not the nutrition and the acupuncture and the meditation and physical conditioning and nutrition and other things that are considered in the integrative therapy category alone. It’s these measures integrated with the novel therapy approaches I’ve mentioned. Now the most important message here is that docs are becoming more and more open to this, and realizing that it really makes a major difference in patients being able to control their own illness. It’s important to share with your caregiver which of the integrative therapies you are using or considering using simply because some of them may interact in an adverse way with some of the medicines you’re getting. That’s the opposite of what we want to achieve.

So an overwhelming yes to use of integrative therapies, and highly believe that they’re useful. However, they need to be used with open knowledge—it’s just as important to have them on your medication list as it is to have the conventional targeted drugs.
LAUREN BERGER:
Thank you for your question, Tracy. And thank you all for your questions. We hope this information will assist you and your family in your next steps.

Slide 52: LLS Resources
If we were not able to get to your questions today, we hope you will call The Leukemia & Lymphoma Society Information Specialists toll-free at 800-955-4572. Or you can reach us by email at infocenter@LLS.org. Our specialists can provide you with information about myeloma research, clinical trials and other questions you may have about treatment, and also questions about financial assistance for treatment.

Please help me thank Dr. Anderson. We are so grateful you have volunteered your time with us today. On behalf of The Leukemia & Lymphoma Society, Dr. Anderson and I would like to thank you for sharing your time with us today. Good-bye and we wish you well.