SLIDE 1: Welcome & Introductions

OPERATOR:
Greetings and welcome to Emerging Therapies for Multiple Myeloma: 2016 American Society of Hematology Annual Meeting Highlights telephone and web education program.

It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you. You may begin.

LIZETTE FIGUEROA-RIVERA:
Thank you and hello, everyone. On behalf of The Leukemia & Lymphoma Society, I would like to welcome all of you.

We have over 1,100 people participating from across the United States and several countries around the world, including Canada, Israel and Norway.

Special thanks to Dr. Paul G. Richardson for volunteering his time and expertise with us today.

Before we begin I’d like to introduce Rosemarie Loffredo, our Chief Administrative Officer and Chief Financial Officer from The Leukemia & Lymphoma Society, who will share a few words. Rosemarie, please go ahead.

ROSEMARIE LOFFREDO:
Thank you, Lizette. I’d like to add my welcome to the patients, caregivers and healthcare professionals attending the program today.

The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer. For more than 60 years LLS has helped pioneer innovation such as targeted therapies and immunotherapies that have improved survival rates and the quality of life for many blood cancer patients. To date, we have invested over one billion dollars in research to advance therapies and to save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

In addition, as this program about myeloma demonstrates, LLS is the leading source of free blood cancer information, education, and support. And we touch patients in their communities through our 56 chapters across the United States and Canada.

LLS also acts as the voice for all blood cancer patients. We advocate for patients, survivors and their families, helping them navigate their cancer treatment and ensuring that they have access to quality, affordable and coordinated care.

We’re fortunate today to have as our presenter, Dr. Paul Richardson, one of the nation’s leading experts in myeloma. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. I’d like to thank Dr. Richardson for providing us today with important information on emerging therapies for multiple myeloma.

Thank you all for joining us and now I’ll turn the program back to Lizette.
LIZETTE FIGUEROA-RIVERA:
Thank you, Rosemarie.

We would like to acknowledge and thank Amgen Inc., Bristol-Myers Squibb, Celgene Corporation, Sanofi US, and Takeda Oncology for their support of this program.

SLIDE 2: Emerging Therapies for Multiple Myeloma: 2016 ASH® Annual Meeting Highlights

LIZETTE FIGUEROA-RIVERA:
I am now pleased to introduce Dr. Paul Richardson, RJ Corman Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Dr. Richardson, I’m privileged to turn the program over to you.

DR. PAUL RICHARDSON:
Thank you so much, Lizette.

It’s my privilege and honor to be on your program today. I’m especially grateful, Lizette, to you and Rosemarie and the whole team at the LLS for doing such a lovely job and bringing everyone together this morning, or I should say this afternoon. And again, it’s an absolute delight to be with you and it’s so nice to hear that we have many patients from not only the United States, but we have patients from Europe and Israel as well on the call or on the webinar today, which is tremendous, and I am very grateful for everyone making their time available for us today.

So, it’s really exciting for me to present on the emerging treatments of myeloma because once again at ASH®, every year we see great strides being made as we go forward in terms of therapeutic options. And my goal for this afternoon’s presentation is to share with our audience some of the excitement around the newer advances in the treatment of myeloma, but at the same time frame that in the context of our understanding of the disease biology and also at the same time to provide hopefully insights for patients and families on the call, or on the webinar I should say, to give them guidance and hopefully provide helpful information in their journey with their disease.

I think the overarching message from the ASH® meeting is continued hope and real progress in our quest to really conquer myeloma in the longer term and make this a chronic illness for the majority. And hopefully in the future be striving towards the cure that we all seek, recognizing that in fairness that remains a goal at the moment. I think it would be an overstretch to say we’ve achieved that; that would be too strong. But I do feel strongly from the data that you’ll see me present today that our treatment options, I hope, are getting us closer and closer to that important goal. But I do also want to make it clear that we have much work to do.

SLIDE 3: Disclosure
Now with that in mind I do have to just show you a couple of other pieces of housekeeping. These are my relevant disclosures, the partnerships I have in terms of advisory roles to respective pharma partners, summarized here.
SLIDE 4: Multiple Myeloma...not just one disease!

DR. PAUL RICHARDSON:
And basically, what I’m going to move first into is a discussion about myeloma itself. And I think the important message to share with everyone is that multiple myeloma is not just one disease. It’s an extremely heterogenous illness that affects people differently. And what’s important to also understand is that within the disease itself, it changes within the patient. So, the tempo and thrust of the illness can vary, not only between patients, but also within the patient. And so, I think one can conceptualize very easily from that how important it is to individualize therapy. We have to, as best as we can, try and tailor our treatment for each of our patients. And that’s an important theme of today’s presentation. And in that context, we try to identify the risks that a patient may face, to recognize that this disease is not only variable between a patient and another patient, but within the patient can be different, and that’s what some of these slides seek – or rather the figures in this slide - seek to demonstrate. And at the same time, because of the advent of novel therapies, we really now are blessed to have the tools to be able to be more nuanced and tailored in our approach to therapy.

SLIDE 5: Importance of Interaction Between Plasma Cells and Bone Marrow for Development of Myeloma

Now, in the next slide I tried to illustrate for you some of the complexities of the biology of this illness. And this shows you a myeloma cell on the left and next to it a stromal cell in the bone marrow that feeds and supports the myeloma cell, and at the same time the bone that surrounds it, illustrated by osteoclasts and osteoblasts. What’s important to recognize in this slide that I borrowed from a very nice review by Dr. Palumbo and my mentor and partner, Dr. Ken Anderson, from a few years ago, in the New England Journal, is to illustrate the complexity of the microenvironment within which myeloma exists. And this is a very important construct because it’s this microenvironment that allows us to specifically target the biology of this illness.

One critical piece that’s missing from this particular slide, and this is because it was published back in 2011, is that over the last five to six years we’ve recognized the incredible importance of the immune system. The immune system has provided us with a new insight into how to really try and tackle this disease. So just to share the principles illustrated by this slide: on the one hand the myeloma is a key target, that’s the cell to the left. The microenvironment is summarized by the stromal cell. And the bone is another key target. And overlaying this is the immune system as a very important therapeutic opportunity as we go forward. And I hope to convince you as we go forward as to how important augmenting and enhancing a patient’s immune system in fighting this disease has become.

SLIDE 6: Natural History of Multiple Myeloma: All Pts Experience Relapse

Now before we get into the nitty-gritty of that, I think it’s important to share with our audience how this disease evolves. Now when we think of myeloma it’s important to recognize that we’ve come to understand that in most patients there is a precursor state that can be identified at varying different times. We call this MGUS for when the protein is at a very low level and not causing any difficulties whatsoever. This becomes more of an issue the older one becomes. And as people live longer, we’re seeing more and more of this entity. The good news is that if you have MGUS about one in four only go on to do something that may
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be worrisome, so three out of four do fine. However, for those one out of four, they typically evolve into smoldering myeloma first and then become active disease.

Now smoldering myeloma has become a very important target. Now in the interest of time today, because there’s lot of information to cover, I’m seeking really to hope to address some of that perhaps in the questions and answers. But smoldering myeloma has become a precursor state where we’re now investing a lot of research and time to try and head this disease off at the pass. Suffice it to say at the ASH® meeting there were some lovely presentations from a number of colleagues, and in particular my partner Dr. Irene Ghobrial, showing that if you target smoldering myeloma you can in fact in higher risk patients impact on the outcome of this illness.

There were also updates importantly from our Spanish colleagues, led by Dr. Maria V. Mateos in which she showed indeed that this smoldering population remain a very important area for therapeutic intervention in a very controlled and structured way at the moment because research again is helping us better understand who benefits from what, when in this setting.

What’s very clear is that when the disease becomes active, so-called active myeloma phase, obviously first line therapy is essential. Now this varies from patient to patient. Younger patients typically receive more intensive, three or four, even five drug-type regimens, and in that context older patients who may be a little more prone to side effects perhaps benefit from slightly less treatment. But what we’re recognizing is that at least three drugs would seem to be the key in the up-front setting in fighting this disease at this stage. And very importantly, the integration of things such as monoclonal antibodies in this early stage of disease may truly influence outcome.

Now what is also very important to share with you is that once you treat active myeloma, the ability to maintain remission becomes very important. And at the ASH® meeting there were a lot of data to support this, that continuous therapy that controls myeloma over the long term is particularly helpful in improving long-term survival for patients.

Now once the disease comes back, which still in 2017 remains the case in the vast majority of patients, we then have a bit more of a fight on our hands. But the very good news is that with new treatments that are evolving, we’re now in a position to take this on and drive deeper and longer remissions yet again. Unfortunately, if the disease comes back after that, it becomes even more challenging. But the good news, in which I want to share some selected examples, is that we have newer drugs and newer agents that are giving us promise even in this more difficult setting for the disease, where the myelomas become even more resistant and more challenging to our approaches.

SLIDE 7: Integration of Novel Agents Into Myeloma Management
Now why can we be so hopeful and so encouraged by recent progress to date? Well, essentially, it’s summarized in this slide. Novel agents have transformed the therapeutic landscape of myeloma over the last decade. But basically, in this context what we’ve seen is that there has been a transformation in prognosis.
DR. PAUL RICHARDSON:
Now, very, very importantly, over the last 13 years, we’ve had no less than 19 FDA approvals with the most recent one being the approval of daratumumab in combination with both lenalidomide and bortezomib, as a legitimate treatment approach in patients with relapsed myeloma. And I’ll show you data in a moment that sort of crystalizes why that’s been such an important advance.

But what I think is important to share with the audience today is that the survival of this disease, whereas unfortunately not so long ago, 15 years or so ago, median survival was two to three years for most people; three to five if one was younger and able to tolerate a stem cell transplant. The really good news is that this has been dramatically improved. And depending on where one is and which country one’s lucky enough to live in which has access to these new drugs - and that’s a relevant consideration I’m afraid because where we have access to novel agents improves outcome is clearly the case - fortunately for most of the people in the audience who are from the United States, we’re very lucky in that regard, and things are getting better; there’s no question. There’s good access to drugs in Israel; there’s good access to drugs in Europe or improving. Some countries still behind there. But suffice to say where there’s access to new drugs and agents, prognosis is being dramatically improved. And I think that of course is the really important message to hear from today’s presentation.

SLIDE 8: Multiple Myeloma survival improving with new drugs: but all patients still relapse after IMiD and PI failure
Now, how so? Well, you can see how in this curve, and I don’t really like showing survival curves for a disease that remains so challenging, but this is important to share with you, just simply to give everyone some really hard information about how much progress has been made. You can see here from the bottom from decades ago, myeloma remained a really very challenging and dreadful illness that was very hard to treat. The really good news over the last 20 to 30 years is steady progress. But what I really wanted to share with you is that despite the progress, there still remain a population of high risk patients in whom there unfortunately can be early mortality. And we still really don’t see a true plateau. But what I’m hoping to show you is that we have clues now, particularly with the advent of monoclonal antibody therapy, that we may be able to achieve a plateau in an increasing proportion of patients. And that I think is, what I find anyway right now, one of the most exciting and promising aspects of what has evolved over the last few years.

SLIDE 9: Poor survival outcomes for patients with advance Relapsed/Refractory MM
One slightly also important point to share with everyone is that once a proteasome inhibitor or an immunomodulatory drug has failed a patient, we’ve realized that the outcomes can be very challenging. And that’s summarized on this slide. But really what I want to do is move away from these kind of bad news slides and say, well, the good news is that despite treatment failure at this stage, we now have new drugs which can really push this back and really improve outcome. So, that’s the positive message here that I really do want you to take away.

SLIDE 10: Multiple genetically distinct subclones can occur in multiple myeloma
Now let’s go back a little bit to biology. In terms of biology, a couple of points to make. As I shared with you earlier, there’s a lot of heterogeneity, as we call it, within the cancer cells that are in any particular patient. This has become a very important phenomenon to better understand because what it means is as opposed
to having one particular cell that’s bad and then many, many, many similar cells that are produced from this one clone, we’ve realized that there are multiple different clones, even within, say, for example, a type of myeloma like IgA kappa disease or IgG lambda disease, that defines the protein characterization of the disease. What it doesn’t tell you is that actually under that umbrella there are multiple different types of that same cell that are malignant.

So, I guess the better metaphor would be for it to think of it a bit like a tree. That you can have an oak tree, but the oak tree unfortunately is made up of multiple leaves, branches, twigs, a trunk, and obviously roots. All of it’s an oak tree, all of its myeloma, the myeloma affecting a particular patient, but there are multiple different facets to it. Roots, trees, branches and leaves. And that’s a relatively innocuous description of the illness. Patients have said to me they think of it more like a basketful of snakes. And that perhaps is true. And where you have many different snakes, but they’re all within a basket and they’re all one type of myeloma. However, you want to metaphorically think about it, I think that’s the way to kind of visualize this clonal heterogeneity issue.

SLIDE 11: WGS at diagnosis
Now the important point is the complexity of this heterogeneity is profound. This is some remarkable from my excellent colleague Dr. Nikhil Munshi, who’s my partner here at Dana-Farber, and Nikhil runs our Correlative Science Team. And as you can see, this is a whole genome sequence of a patient’s particular myeloma. So, this is not the patient, this is their cancer. And this particular cancer diagnosis shows, and you can see it in the top right hand area of the slide, the substitutions or the number of mutations that there are at diagnosis in this particular patient’s myeloma, are over 5,000. Now that’s at diagnosis. Now this patient fortunately went on to successful treatment, induction remission treatment, maintenance and so forth as part of one of our clinical trials.

SLIDE 12: WGS at relapse
When this patient then relapsed, unfortunately, what we saw was the following: that the number of mutations had dramatically increased in their disease. And as you can see at the top, we have now over 12,000 mutations. So, this is very sobering because what it tells you is that the genetic instability of this disease is profound, that there are multiple mutations, multiple changes, and that these get worse over time. And these are, of course, all specific to specific genes. And this makes the challenge of targeting any one particular mutation quite obvious because obviously if you’re doing one or two mutations, that’s a relatively easy task. If you’re dealing with 12,000, that’s actually quite challenging.

So, the bottom line here is I think that we need to recognize that this disease provides us with a substantial challenge because it’s so genetically unstable, but at the same time there are therapeutics opportunities and I’m going to show you these in a moment. And they’re nicely summarized in this next slide.

SLIDE 13: Multimodality targeting of MM in the context of the BM microenvironment
This is a schematic from a paper we published about a year or so ago, to show you that there is a multimodality approach to targeting myeloma and we do so in the context of the microenvironment, as I alluded to before. Now there’s a very strong reason for this because if you think of the previous slide you can understand why we have to throw a very big net around this disease to shut it down. And you can see
DR. PAUL RICHARDSON:
summarized in this very nice cartoon that we seek to do this in a multitude of ways. Not just targeting the tumor cell itself, but targeting all aspects of the neighborhood. And very, very importantly, now going after the immune system. Because the exciting thing about the immune system in particular is that it doesn't care about these mutations. An activated T-cell that knows what it has to do can kill a myeloma cell irrespective of the mutations it may have. It really doesn't matter what the genetic instability of that tumor cell may be because a T-cell can knock it out regardless.

Now set against that, of course, are the fact that other drugs we have in our armamentarium are also incredibly effective at doing this. They include the proteasome inhibitors, the immunomodulators, in particular what we call the second and third generation immunodulators, and in that same context now the monoclonal antibodies.

SLIDE 14: Rational combination strategies in relapsed, refractory MM
So, this next slide just illustrates the concept that if you can add to our current platform of combination approaches, next generation IMiDs, next generation proteasome inhibitors – I show here carfilzomib and ixazomib and then when one throws on top of that monoclonal antibodies, one can really make a difference in terms of outcome.

SLIDE 15: Options in Relapse - NCCN guidelines 2016
Now moving onto the next construct is a summary of the treatment options we’re lucky enough to have in the United States. And this is a summary from the 2016 NCCN (National Comprehensive Cancer Network) Guidelines on the treatment of relapsed refractory myeloma. I show this slide just to illustrate that the good news is that for all the challenges I’ve just illustrated to you, we have a good series or multiple, multiple weapons that we can use to bring to bear. And this armamentarium continues to be added to.

SLIDE 16: New Directions: Key Targets in MM
The next slide I want to show to you what our particular targets are. Well, the key targets in myeloma are targeting what we call protein degradation, that’s what a proteasome inhibitor does. Synergistic strategies to try and bring these things together. Strategies such as immunomodulators, so-called histone deacetylase inhibitors, other small molecules. Very importantly, a very exciting new BCL1 inhibitor called venetoclax, which was very exciting at the meeting, targeting specifically an abnormality called 4;14 and a translocation of a chromosome. And then all sorts of other exciting and interesting small molecules that can synergize with this excess protein production approach.

Now as I mentioned targeting genomic abnormalities, and I touched on one drug that does seem to do this in a subset of patients, venetoclax, it’s very important to recognize, though, that combination therapy absolutely matters. Because as you can understand, one mutation is all very well, but what really matters is what can you throw around the mutation that shuts down all the others. And then we come to this whole concept of immune suppression. If we can restore anti-myeloma immunity, we can actually teach the immune system to memorize what it needs to fight, be it through vaccines in very early stage disease, or cellular therapy such as the so-called CAR-T approach, later in the illness perhaps. You can understand how these strategies could be evolving or emerge to really improve outcome.
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SLIDE 17: Rationale: Preclinical Combination of Lenalidomide (Len) + Bortezomib (Bz)

DR. PAUL RICHARDSON:
So, let’s start with some very basic, simple strategies and premises. Basically, one example of this is the synergy between a proteasome inhibitor and an IMiD. And I especially want to acknowledge my laboratory colleagues, Dr. Constantine Mitsiades and Dr. Teru Hideshima from our own group, who really pioneered this some years ago - now over a decade ago in fact - where they combined lenalidomide with bortezomib and were able to show that even in resistant myeloma that had become resistant to bortezomib, you could overcome that resistance by adding lenalidomide.

And I’m especially grateful to patients who are willing to allow us to take samples from their bone marrow to do this. Because as you can see from this slide, we have patient-derived myeloma cells – that we then use to test in the laboratory what this synergy may be. Without patients being willing to provide these samples, we would never know better. And so, in this context it’s especially nice to show you this slide because you see not only the importance of laboratory observation, showing how we might rationally combine drugs, but we also see the very important contribution of patient samples to this process and how that generosity results in true advancement of science.

SLIDE 18: Journal Articles

Now in that same context what did this lead to? Well, very quickly this was translated to the bedside. We were able to take this into the clinical trial setting and again this is just a representative example of a number of papers that were published from a series of studies that we did. And again, many other folks have done this in different settings. I just show these three major papers as an example of how this really helps us move the field. And I especially want to acknowledge the patients who participated in these particular trials.

So, this combination strategy resulted in a dramatic advance in terms of understanding that the combination of lenalidomide, bortezomib and dexamethasone combined was highly synergistic both in relapsed myeloma and very importantly in the up-front setting as well.

SLIDE 19: ASPIRE Study: Carfilzomib + lenalidomide + dexamethasone
Primary endpoint - PFS

Now other studies have shown just the same thing. Perhaps one of the most exciting and important and has been carfilzomib combined with lenalidomide. This study, the so-called ASPIRE study, done in relapsed disease, showed a dramatic improvement in outcome when carfilzomib was combined with lenalidomide and dexamethasone in these relapsed patients. And there was a substantial improvement in the time of disease control when carfilzomib was used. So, this was an important validation, that when you combine a proteasome inhibitor and an IMiD, you see true synergy.

What’s really interesting is that some of the preclinical data that has since emerged might have not suggested that actually from profound mechanistic strategies that were done actually and published some years ago. What’s really interesting is in fact clinically now and from the model systems that I just showed you, we’ve actually shown this is clearly a synergy that matters. And so, there is no more debate about this other than to recognize that this platform of proteasome inhibition plus immunomodulation has been
DR. PAUL RICHARDSON:
transformative as a backbone approach to therapy. And that’s why for many on the call today, you’ll have been talking to your doctors about proteasome inhibitors, be it bortezomib, carfilzomib, ixazomib or others, and you’ll have been talking about lenalidomide, which is a backbone agent in myeloma now, at diagnosis and in maintenance, and of course other immunomodulatory drugs like pomalidomide in relapse, and using them very much in combination. So, this is a very important premise.

SLIDE 20: TOURMALINE-MM1
Now another study that illustrates this point and actually validated the same model, is the use of ixazomib with lenalidomide and dexamethasone. This paper was published last year in the New England Journal of Medicine and in fact illustrated very nicely that when you combine three oral agents in this category you see significant clinical benefit as illustrated on this slide.

SLIDE 21: TOURMALINE-MM1
Phase 3 study of weekly oral ixazomib plus lenalidomide-dexamethasone
Final PFS analysis: Significantly improved PFS with IRd vs RD
What’s very important is there’s about a six-month gain, it’s all just pills, and it’s very well tolerated and very excitingly it not only conveys benefit in patients with standard risk as we call it, but in patients with high risk this combination was particularly effective, as it is with carfilzomib and as it is with bortezomib. So again, this genetic high risk group are well served by this approach, which obviously is an important thing.

Now how can we build on this? Well, if I was to share with you all the concepts that are under study we’d be here until tea time this afternoon. But what I’m going to try and do is drill down on some important concepts. And the first one I’m going to share with you is the emerging story around histone deacetylase inhibitors.

SLIDE 22: Pan-DAC Inhibitors: Mechanism of Action
Pan-DACi inhibit a broad range of deacetylase enzymes: target both histone and nonhistone proteins involved in oncogenesis
Histone deacetylase inhibitors are a very exciting new class of drugs. This is one example, so-called panobinostat, which in fact inhibits deacetylase inhibition within the genetics of the cancer, but also has this other effect on the so-called aggresome which is an escape pathway that the cell uses when the proteasome is inhibited.

Now this mechanism of action, which is actually complex, attacking both the genetics of the cancer as well as the protein degradation pathway, has been actually leveraged now to generate an FDA approved platform of panobinostat plus bortezomib, and indeed now plus immune modulatory drugs. What’s really exciting is we now – and this was actually presented at the ASH® meeting – we have next generation histone deacetylase inhibitors, including a very exciting molecule called AC241, which is better tolerated it seems perhaps than panobinostat. And is very excitingly very active, particularly with the IMiD platform. So, this science has really gone forward.
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SLIDE 23: Journal Articles

DR. PAUL RICHARDSON:
I’ll just show some exciting examples and some representative papers. These are several papers of the PANORAMA program that published over the last several years, and illustrate very nicely how this combination is highly synergistic.

And what I wanted to emphasize in particular was the 2016 paper that we published last year that illustrated that in a particular subgroup of patients, clinical benefit was seen that really was important to share.

SLIDE 24: PANORAMA 1 Study: Panobinostat + bortezomib + dexamethasone

Primary endpoint - PFS
On the one hand with the broader study, patients gained from the addition of the histone deacetylase inhibitor an average of around four months of clinical benefit in terms of disease control, which I know may not sound like a lot, but as an average that’s substantial.

SLIDE 25: PANORAMA 1 Study: PFS subgroup analysis – Prior IMiD + BTZ with ≥ 2 Prior Lines
When one looks at the next group of patients, in other words those patients in whom an immunomodulatory treatment and bortezomib had failed them, if you look at that, this group of patients enjoyed a seven-month improvement in disease control when adding panobinostat to this platform. So, this data has been particularly compelling and I think helps us understand why this class of drug, and in particular the next generation of histone deacetylase inhibitors, the so-called AC241 and other type family of molecules, they actually target HDAC6, which again not to worry people about the science too much, but just to know that it’s a more selective targeting, we think holds great promise. So very exciting data from the HDAC inhibitor class and recognizing that panobinostat is FDA approved and of course is approved in a variety of different settings, not least in the United States, but also around the world. And so, we’re very pleased with the performance of this particular class of drugs.

One thing to emphasize, if I perhaps didn’t say earlier, is that these are typically given orally. These are pills as opposed to injections.

SLIDE 26: Restoring Immune function:
Now let’s now move on and think about other advances at the ASH® meeting that are very relevant. Well, I want to spend a little bit of time on the immunomodulatory drugs. I’ve already talked about how the HDACs have its own benefit. I should mention one thing, that they do also appear to have an immune effect as well. But I really want to spend time on monoclonal antibodies, immunomodulatory drugs, checkpoint inhibitors, and then touch on cellular therapies.

As a first point of starting, I want to tell you a little bit more about the immunomodulatory drugs and frame that in the context of what we heard at the ASH® meeting.

SLIDE 27: Lenalidomide and Pomalidomide in Myeloma
In terms of the lenalidomide and pomalidomide story, we recognize that these drugs are very important in not only targeting the myeloma cell, but also very importantly targeting that neighborhood that I alluded to
DR. PAUL RICHARDSON:

earlier. But I really want to show this slide to illustrate the fact that we now understand that these agents particularly target the immune system and stimulate dendritic cells and stimulate very importantly natural killer cells and T-cells in their fight against myeloma. This has been a very, very key concept.

How does this happen? Well, recent science has suggested this worked through things called Ikaros and Aiolos. These are very important pathways of transcription factor breakdown, that if they are inhibited, as they are here, you can see a direct outcome and then you can see a collateral effect of the drug, where you have a very direct effect on the immune system, not only on multiple myeloma cytotoxicity itself, but also on the immune system. This is a very important concept to grasp. And recent data continues to support that and there was plenty of data at ASH® that also continued to support this concept, that these immunomodulatory drugs basically costimulate T-cells via the targeted degradation of these so-called transcription factors Aiolos and Ikaros. Very, very important simple concept in some ways, but very interesting and important because it helps us identify why these drugs work.

SLIDE 28: Immunomodulatory agents IMiDs: mechanism of action

Now important message to share with you is that this approach has resulted in our further understanding of how to develop next generation immunomodulatory drugs, also called IMiDs.

SLIDE 29: Model of Lenalidomide and Pomalidomide Co-Stimulation of T Cells via Degradation of Aiolos and Ikaros

The most practical example of that is the pomalidomide story, which is summarized on the next slide. And this basically shows the example of pomalidomide combined with lenalidomide and dexamethasone or used with low dose dexamethasone. These are very effective and powerful platforms. The data are summarized here.

And I just want to show this slide to illustrate the point that the use of these combinations in relapsed-refractory myeloma can be very, very active. And indeed, they result not only in activity, but they also improve outcome by improving progression-free survival.

SLIDE 30: Journal Articles

What's very important to understand, and this is the message that was at the ASH® meeting in San Diego in December, is that beyond pomalidomide and exciting as pomalidomide is and as important as it is in relapsed-refractory disease, we have now next generation immunomodulators that are entering clinical study.

SLIDE 31: Efficacy Results of POMALIDOMIDE + LoDEX in advanced RR MM (Phase II/III: MM002 & MM003)

What these drugs are hoping to do is build yet more upon the success of first thalidomide, then lenalidomide, most recently pomalidomide.

SLIDE 32: MM-003 Study: PFS

And the good news for patients is that we'll have these next generation IMiDs available. And what they have the promise of is being even more selective. Ideally, although the tolerability profiles of the IMiDs tend to be
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DR. PAUL RICHARDSON:
fairly good, even less in terms of side effects and even more active. So again, a very exciting new direction
that continues to evolve.

SLIDE 33: Monoclonal Antibodies Kill MM Through Multiple Mechanisms
So now I’m going to change gears a little bit and focus on monoclonal antibodies. In terms of monoclonal
antibodies, it’s important to recognize that there are a variety of ways that monoclonal antibodies work.
Monoclonal antibodies have been around for some time in the treatment of lymphoma, but it’s fair to say in
myeloma that they’ve been a long time coming and a lot of blind alleys unfortunately have been gone up
with antibodies, where sadly for a variety of reasons we’ve not been as successful as we’d hoped.
The really good news is over the last five to ten years that has dramatically changed, and how so? Probably
primarily by the identification of valid targets to which the antibody goes, and at the same time the
sophisticated engineering of the antibodies themselves to make them more effective and safer to use.

SLIDE 34: MAb-Based Therapeutic Targeting of Myeloma
Now how do antibodies work? Well, they have direct effects where they interfere directly with the survival
of the myeloma, or they can actually deliver a payload to the myeloma. That can be a little bit more
challenging, associated with slightly more toxicity, but I’m going to show you data that suggests it can be
very effective. And then there are these indirect effects where it activates complement, where they basically
label myeloma cells for killing by natural killer cells, and they activate T-cells by taking the brakes off as it
were, the effects on T-cells.

Now the interesting thing there, of course, is the role of checkpoint inhibitors in that same strategy and we’ll
come to that a little bit later. But suffice to say, through those direct effects and indirect effects, antibodies
can be highly effective, and very, very importantly, they don’t care about the genetics, they will go after the
cancer regardless of whatever mutations it may have.

SLIDE 35: Elotuzumab: Immunostimulatory Mechanism of Action
So, in that context what about the targets? Well, this is a slide that seeks to summarize some of the targets
that we have. I want to focus primarily on the so-called SLAMF7 target, or CS1 as it was originally called,
CD38 which has been really quite remarkable, and then perhaps touch on, in brief, that there are a variety
of other targets, such as CD138 and DKK1 and others, and indeed IL-6 for that matter, that may have promise in
the future.

But for the interest of time, and to give you a message that’s digestible this afternoon, because obviously,
there’s so much information to share, I really want to focus perhaps on SLAMF7 and CD38 primarily.

So, let’s talk a little bit about SLAMF7. Well, SLAMF7, which actually stands for signaling lymphocyte
activation molecule F7 – please don’t worry about that, but that’s the way it’s categorized – SLAMF7 is
very interesting because it’s very, very specific to myeloma. It’s highly expressed by myeloma and it’s also
expressed by natural killer cells. And the most important antibody in this space, elotuzumab, which is now
FDA approved, does, is it targets SLAMF7 and it does so both on the natural killer cell, which is illustrated at
the top here, and it directly activates them, but it also targets the myeloma cell. Now the good news is that
DR. PAUL RICHARDSON:
when it targets the myeloma cell it doesn’t in fact activate it. What it then does is it actually targets it, but there is no mechanism by which there’s activation. Because obviously if you activated the myeloma cell that might not be a good thing. The good news is, though, that you can tag it because the antigen is expressed on the myeloma cell.

Now if you activate the natural killer cell next to it, that actually results in a remarkable thing. The natural killer cell is turned on, but also then goes after the myeloma cell. And what’s really important is that when you add to this mix a so-called immunomodulatory drug, an IMiD, as I just alluded to, be it lenalidomide or even pomalidomide for that matter, the whole thing gets turned on dramatically because as I mentioned before, the immunomodulator stimulates the T-cells and the natural killer cells. So, by doing this the whole system gets very, very activated and can be very effective.

SLIDE 36: ELOQUENT-2: Primary Analysis
And how do we know that? Well, the next slide illustrates the point that if you combine elotuzumab with lenalidomide you can substantially improve outcomes as illustrated in this slide, showing that progression-free survival was substantially increased by the addition of elotuzumab to lenalidomide and dexamethasone. This was a large international randomized trial that led to the FDA approval of elotuzumab as an antibody in this setting.

SLIDE 37: Elotuzumab in High-Risk Patients
What’s very important to share with you is that elotuzumab was able to overcome the adverse effects of bad genetics, 4;14 on the right of the slide, 17p which is a marker of particularly resistant disease on the left. And you can see that there was a substantial improvement in clinical benefit in these high-risk patients. That was very exciting.

SLIDE 38: Elotuzumab + bortezomib + dexamethasone: PFS
What’s also very important about elotuzumab is if you combine it with bortezomib you can see substantial improvements in outcome as well. So, when you combine elotuzumab not only with lenalidomide, but also with bortezomib, results could be very potent. And what we heard about in preliminary form at the ASH® meeting this last December was that indeed these data continue to look very promising and most importantly what we also heard about was that elotuzumab plus lenalidomide plus bortezomib and dexamethasone, the so-called RVD-elo, preliminary results from these studies are very promising and more data will follow and you’ll hear more about this over the next year or so. But this particular platform is very exciting.

We also hear that elotuzumab used early in smoldering disease can be very well tolerated and my partner Dr. Irene Ghobrial showed a very nice combination study of elo-RD used in smoldering myeloma being particularly effective. So, this was a very exciting set of data which really confirmed what we had felt would be the case, that smoldering disease in particular might benefit from an antibody-based approach early, particularly with a well-tolerated antibody like elotuzumab, which generally speaking is very well tolerated in terms of side effects.
SLIDE 39: Daratumumab: Mechanism of Action

DR. PAUL RICHARDSON:
Now what other big news were there in the antibody space? Well, this next slide seeks to summarize that. This is of course daratumumab. And this arguably was the most exciting data presented at the meeting overall, the data around daratumumab, what news do we have of daratumumab?

Well, basically in the context of daratumumab, just to share with you a couple of ways this important antibody works, not only does it target the myeloma itself, but it also has a multitude of immunomodulatory actions and in the context of its on-tumor actions, there is this activation of complement, this activation of the T-cell mediated response, but very, very importantly there’s this phagocytic mechanism and this apoptotic mechanism, where there is a direct killing of the tumor cell as summarized on this diagram.

Now we know from published data and as shown on the next slide, that daratumumab as a single agent is extremely active.

SLIDE 40: Journal Articles
This led to the FDA approval of daratumumab on an accelerated pathway in 2015. The full approval of daratumumab has followed this year, in combination, largely informed by the following information.

SLIDE 41: Synergistic with Other Standard MM Therapies, Including Bortezomib and Lenalidomide
That when you combine daratumumab with other drugs like lenalidomide and bortezomib, you see synergy. Please don’t worry about the details of this summary, but just to show you on this slide that when you combine daratumumab with lenalidomide it’s dramatic. When you combine it with bortezomib it is dramatic. And when you put all three together, myeloma is very uncomfortable and hates it.

SLIDE 42: Journal Article
Now the good news is in terms of clinical studies, we have clear evidence that this is the case. This is data showing that when you combine daratumumab, bortezomib and dexamethasone in myeloma there’s tremendous benefit. This paper was published by my dear friend and colleague Dr. Antonio Palumbo earlier in 2016. What’s really exciting at the ASH® meeting is that this was presented in updated form and we were able to show that this benefit is dramatic.

SLIDE 43: Updated Efficacy; ASH® 2016
And what I want to show you, and this is from a presentation from Dr. Maria V. Mateos, where she showed beautifully that in fact you can see a real plateau starting to emerge in this relapsed-refractory population and that responses continue to deepen with longer follow up. So, this is a tremendous result and very, very supportive of the FDA approval that we saw earlier in 2016.

SLIDE 44: Conclusions
And the conclusions were that there were higher complete response rates with daratumumab-based platforms, MRD negativity was striking with this approach, and further support the use of this newly approved regimen in relapsed-refractory myeloma, with the most benefit in patients with one line of therapy. So, the idea is move this drug earlier.
SLIDE 45: Journal Article

DR. PAUL RICHARDSON:
Now what about when you combine daratumumab with lenalidomide? Well, the results are dramatic as well. And this data was presented in updated form by Dr. Saad Usmani at the meeting, at ASH® in December. I show here the publication from the study group as a whole which we published in the New England Journal earlier last year.

SLIDE 46: POLLUX: Study Design
Just to remind people of the study design. It was the combination of daratumumab, lenalidomide and dexamethasone compared to the gold standard, which is RD. And the basic take-home message is that the three drugs clearly out-performed the two. And if you look at this, and I show this because I think this is the most striking, and Dr. Usmani’s presentation affirmed that this is sustained.

SLIDE 47: POLLUX: Progression-free Survival
The progression-free survival is dramatic, it’s not been reached, and very, very importantly you can see here what I was alluding to earlier in my presentation, which is a strong hint of a plateau. So, a monoclonal antibody approach combined with immunomodulatory treatment or bortezomib results in really dramatic results in the relapsed-refractory setting. And so, the goal is if we move this earlier, what will we see?

SLIDE 48: Overall Response Ratea
Now just to show a few more other points about data. If you look at the response rates, they’re summarized here, they’re really quite dramatic.

SLIDE 49: Updated Efficacy; ASH® 2016
If you then look at the summary of the updates from ASH®, and as I mentioned this was presented by Dr. Usmani, you can see that the median is still not reached and that plateau still is looking provocatively possible.

SLIDE 50: MRD-negative rate; ASH® 2016
And at the same time one then moves to the MRD negative rate, which is this experimental tool where we look at what we call minimal residual disease negativity, you can see that rates of MRD negativity are substantially higher for the three-drug platform of DRD or daratumumab, lenalidomide, dexamethasone, than the control treatment of RD, which was previously a gold standard.

SLIDE 51: OS; ASH® 2016
There’s one last slide to show, which is overall survival data. And as you can see, whilst it’s not quite yet significant, it’s heading very strongly in that distance and the curves are beginning to separate. But these data are preliminary, so I think we need to be very careful before we can draw too much in the way of conclusions from that.

SLIDE 52: Conclusions
But suffice to say, the clinical benefit of daratumumab-based therapy remains very powerful.
**SLIDE 53: Lenalidomide-based studies**

**DR. PAUL RICHARDSON:**
So how does this compare to other trials? Well, very important point to share with you is these are unprecedented results, that essentially what we’re seeing is that lenalidomide-based therapies continue to be a gold standard in the relapsed-refractory setting. When you combine them with proteasome inhibitors, be it ixazomib or carfilzomib, the results are phenomenal. Particularly striking for carfilzomib. Ixazomib, which is very well tolerated, also looking very promising. As I already mentioned, elotuzumab really does enhance lenalidomide.

But then one looks at what daratumumab does, you can see that there is a quantum leap. And what do I mean by that? Well, the quantum leap I showed on the pictures before, but if you look at a thing called a hazard ratio, the smaller the number the better. And as you can see, in the myeloma space we’re used to hazard ratios of around .7. And that’s very good, that means these drugs really, really work. If you look at the daratumumab hazard ratio, it’s down to .37. And that really says an awful lot. It says that we’re seeing a dramatic improvement in our ability to control disease for longer with the use of these antibodies, and that of course is very good news.

**SLIDE 54: PAVO Study Design; ASH® 2016**
Now how are we trying to take daratumumab forward? Well, there are a number of strategies that are currently under study. The most important one that was shared was the idea of how can we make daratumumab infusions more convenient. And there’s a big effort now to look at subcutaneous administration of daratumumab with the goal of improving patient outcome. And again, the details I think probably I can move over quickly in the interest of time.

**SLIDE 55: IRRs: ASH® 2016**
But suffice to say what we’re able to show is that when you combine or rather use this subcutaneous approach the side effect profile is very acceptable, very manageable in the big picture. The characteristics of the way the drug behaves are satisfactory.

**SLIDE 56: Dose Mean (SD) Profiles: ASH® 2016**
What we call the PK is also satisfactory.

**SLIDE 57: Simulation of Mean Concentration-Time Profiles of DARA Following SC and IV Dosinga**
This is a beautiful graphic from Dr. Usmani showing this effect, that you’re getting enough drug, just administering it subcutaneously.

**SLIDE 58: ORR**
But very, very importantly the efficacy is excellent and the dose does appear to matter, but it seems to be very similar to what we would observe with intravenous daratumumab.
SLIDE 59: Conclusions: ASH® 2016

DR. PAUL RICHARDSON:
So basically, our hope is that daratumumab can be given subcutaneously safely and it can be therefore much more convenient for patients, and that we can then study it as we go forward in different combinations and make headway.

SLIDE 60: Is there a role for ectoenzymes in this intricate network?
Now this next slide illustrates a very interesting and important point, that in fact there are a number of growth and survival signals that in this ectoenzymic approach to the treatment of myeloma, that we need to pursue. And what do I mean by that? This ectoenzyme is the thing that's expressed on the cell surface that may be very, very relevant to enhancing the anti-myeloma effect of what we're doing. And this particular paper, by Dr. Dhodapkar from Yale, is very important because it illustrated this point.

But I think the next graphic below it is particularly relevant because that shows you how this ectoenzymic intricate network works from a real leader in the CD38 field, a man by the name of Dr. Fabio Malavasi.

SLIDE 61: ASH® 2016 – ISA POM DEX (Richardson PG et al.) Introduction
And point is just to illustrate this, and Fabio is actually is a very close colleague and personal friend, is that he’s dissected beautifully the complexity of the mechanism through which CD38 works. The good news is that in addition to the way DARA work, we have other antibodies in this space that are showing great promise. And one of the most exciting is isatuximab. This is a similar antibody to daratumumab, but it has a shorter infusion time and it does appear to also be more active in this ectoenzymic space. And that’s illustrated on this graphic.

In our work with this particular molecule, because we’ve obviously worked very hard with daratumumab and we’ve now worked now with isatuximab together with other investigators, is to basically show that this is really very, very active.

SLIDE 62: Results: Paraprotein reduction
This is a so-called waterfall plot, which shows that this is very effective in treating the patients who got this combination of isatuximab and pomalidomide. And what we were able to show as well is that these responses were durable, that they lasted. So, this was very, very exciting.

SLIDE 63: Results: Time on treatment
In that same context, when we basically combined pomalidomide with it, we were able to illustrate that the combination was well tolerated and going forward the response rates were dramatic.

SLIDE 64: Summary
Two-thirds of patients who were relapsed-refractory appeared to respond very nicely to this. So, we’re very pleased by this and looking forward to going forward with this combination in what we call a large Phase III trial that is just about to be launched.
SLIDE 65: Anti-CD38 antibody-mediated therapy in myeloma: some unbeaten paths of potential application

DR. PAUL RICHARDSON:
Now this is more work from Dr. Fabio Malavasi, presented at the ASH® meeting, which I wanted to share. First and foremost was that are there more ways that we can further exploit the CD38 target. And what I really want to share with you there was that this CD38 target remains a very important space into which we are exerting a lot of research effort because we’re beginning to recognize that there are a number of important complexities to this area that may be open to therapeutic strategy. So, this is really very, very good news.

And basically, going forward I would just simply say to you that there are going to be some remarkable, I think, some remarkable processes or rather remarkable progress in this whole area.

So, let’s change gears a little bit and look now at other antibodies that target different, what we call different antigens in this disease.

SLIDE 66: First in Human Study with GSK2857916, An Antibody Drug Conjugated to Microtubule-disrupting Agent Directed Against B-cell Maturation Antigen, in Patients with Relapsed/Refractory Multiple Myeloma: Results from Study BMA 117159 Par1 1 Dose Escalation - ASH® 2016
One of the most exciting, I think, is the so-called BCMA target, B-cell maturation antigen. And I want to share some beautiful work presented by Dr. Adam Cohen. We are part of this study group with some wonderful colleagues, all summarized here.

SLIDE 67: Background
And this is a very interesting antibody. It’s an antibody that takes with it a payload. What I mean by that, it’s almost like a guided missile. It’s a missile that hits this particular target, BCMA, but brings with it a particular warhead that can be very, very, very damaging to the myeloma.

The science is summarized on the next slide.

SLIDE 68: Maximum % Change in M-Protein or Free Light Chain
And basically, what you can see is that the BCMA is an important target in myeloma and that this particular antibody, because it brings with it this disrupting agent, this warhead called MMAF, can be very, very, very potent.

Now what we’ve shown in our trial and was presented as an oral presentation at the ASH® meeting, is as follows.

SLIDE 69: Part 1: Summary of Clinical Activity and Duration on Study
There was dramatic response rate seen, that these response rates were viable, and what was really important, they were durable.
SLIDE 70: Conclusions

DR. PAUL RICHARDSON:
There were some side effects. This is not as easily tolerated as, for example, dara or isatuximab. But having said that, it’s extremely active. And what we were able to show was that in advanced myeloma 67% of patients responded to this approach. These patients were not just advanced in terms of a lot of disease, they were heavily pretreated and highly resistant. So, in that context we think this is a very promising new approach.

SLIDE 71: Immune Suppressive Microenvironment in MM
Now in the last few minutes I wanted to next focus on the checkpoint inhibition story because that I think is very exciting and good to share.

What do I mean by checkpoint inhibition? Well, this is the ability to put brakes on your T-cells. And what has happened in myeloma is our recognition, just as it has been beautifully delineated in solid cancers like melanoma and lung cancer, the immune system is selectively turned off by the cancer and hence the growth of the tumor. In myeloma, the same turnoff happens. These same brakes are applied. Well, the very good news is that you can inhibit these brakes, take the brakes off, and get the T-cells activated again.

SLIDE 72: Phase 1 Study of Nivolumab in patients with relapsed or refractory lymphoid malignancies - Preliminary Results
And there are a number of important efforts underway now to explore this approach in myeloma and they’re summarized here. This is multiple myeloma, you can see Phase I studies of nivolumab, which is obviously a very important new checkpoint inhibitor that’s now FDA approved for a number of solid cancers. It’s called Opdivo® and many of you may be familiar with it because of that name. But suffice to say nivolumab as a single agent in myeloma, not particularly active, but when you combine it with other drugs, particularly the IMiDs, things really get turned on.

SLIDE 73: Lenalidomide enhances checkpoint blockade-induced multiple myeloma cytotoxicity
And at the meeting we were able to see a lot of exciting work, looking at particularly the combination of another checkpoint inhibitor, so-called pembrolizumab, which also targets PD-1, which is this important checkpoint inhibitor. And when you add lenalidomide to it, it really goes into overdrive. And the results from these studies suggest real promise to this approach.

SLIDE 74: Pembrolizumab and the PD-1 Pathway
Our first clue came from this in a number of studies that were presented at the 2015 ASH® meeting, at this particular ASH® meeting there were more updates suggesting that this particular approach continues to be very, very promising.

So, at the present time there are a number of studies ongoing. One of them is summarized here, that pembrolizumab combined with lenalidomide and dexamethasone is now underway and moving forward. And this is a very exciting new area which we think is showing great promise.
SLIDE 75: Ongoing Clinical Trials Evaluating Checkpoint blockade in Combination with IMiD in Myeloma

DR. PAUL RICHARDSON:
And at the ASH® meeting, as I mentioned, there were some updates presented. This particular update was from my colleague Dr. Ashraf Badros. Dr. Badros showed very nicely very high response rates in very resistant disease, which appeared very durable.

SLIDE 76: Pembrolizumab + REV/DEX
And the important point is here there are some side effects to these immune system drugs, some of it being lung injury, which one has to be a bit careful with, as well as things like hypothyroidism. But the good news is, generally speaking these are very manageable.

SLIDE 77: Pembrolizumab in Combination with Pomalidomide and Dexamethasone for RR MM
So, takeaway here is that basically the use of PD-1 inhibitors like pembrolizumab, like nivolumab, are really showing promise going forward in myeloma.

SLIDE 78: ASH® 2016: Durvalumab in MM – Combos with DARA, POM, DEX
Now what new ones do we have on the horizon? Well, at the ASH® meeting there were a lot of meetings discussing this new PD-L1 inhibitor, durvalumab, which we now are studying in combinations with daratumumab, pomalidomide and other approaches that are showing great excitement as we go forward.

SLIDE 79: Harnessing the Immune System to Fight Myeloma: Types of Immunotherapy, Immuno-Oncology
So, in the last couple of minutes I want to touch now on the other aspects of how we enhance the immune system. We’ve talked a lot about antibodies and checkpoint inhibition. I do want to emphasize that vaccines are showing great promise in this setting and there were a number of presentations on the promise of vaccination strategies, particularly in smoldering disease where you can actually look to enhance memory. What’s very important to also recognize is the excitement around what we call CART-cells. These are so-called chimeric antigen receptor T-cells, where essentially what one does is take these cells outside of a patient and educate in the context of appropriate cellular manipulation, educate these T-cells on the targeting of the patient’s myeloma, infuse them back and give them back to the patient in a way in which these T-cells can then be particularly activated against the patient’s myeloma.

SLIDE 80: Myeloma CAR therapy- ASH® 2015 - 2016
And what did we hear about myeloma CAR-T therapy at the meeting? Well, in summary, from the previous meetings we had seen some dramatic results targeting CD19 and that’s summarized here.
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SLIDE 82: B-cell Maturation Antigen (BCMA)-specific chimeric antigen receptor T cells (CART-BCMA) for multiple myeloma (MM): initial safety and efficacy from a phase 1 study

DR. PAUL RICHARDSON:  
But what was really interesting was to see what came from the BCMA study, presented by Dr. Adam Cohen and his colleagues from the University of Pennsylvania, U Penn, with Dr. Ed Stadtmauer as the senior investigator in these trials.

SLIDE 83: BCMA (TNFRSF17, CD269)  
And what you can see here from this particular presentation, and again in the interest of time I’ll move through it relatively quickly, but they used the BCMA target.

SLIDE 84: BCMA-specific CAR T cells  
Which is very important, they used a classic CAR-T technology to be BCMA specific in their targeting.

SLIDE 85: Patient Characteristics – Cohort 1 (n=9)  
And at the same time they then were able to bring onboard a number of patients, highly selected, and recognize please this is a small number, so it remains very preliminary, but of the nine patients who were able to get into this clinical trial and receive therapy as planned, they had obviously, unfortunately, had all the effective treatments that we really have, lenalidomide, bortezomib, pomalidomide, carfilzomib, transplant, daratumumab even in 40% of them, and even checkpoint inhibition, and what we were able to show is that in these patients, in whom all these other treatments had unfortunately run out of steam in helping them, they were able to see some dramatic results.

SLIDE 86: Safety (n=9)  
Now what about safety? I do want to share this with you because I think the enthusiasm around CAR-T therapy is well-founded, but we have to also be very realistic about side effects. One of the most important side effects is the so-called cytokine release syndrome (CRS) that occurred in the majority of patients, almost all, and can actually be very challenging and require hospitalization to ensure that patients are safe. We also have to use specific antibodies that shut down some of the cytokines that drive it and this is obviously relevant. One of the more scary side effects, unfortunately, is this posterior reversible encephalopathy syndrome. Fortunately, this only occurred in one patient, but the good news was that this patient made a full recovery, so that was encouraging.

SLIDE 87: Clinical responses  
Now what about the efficacy? Well, this is summarized here. As you can see in this incredibly sick population of patients in whom their treatments had really run out of steam and/or failed them, we saw some remarkable responses. So, I think recognize this is a highly-selected group of patients, this represents we think a very, very important new direction of therapy and may be for selected patients a key strategy going forward.
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SLIDE 88: Integration and Impact of Novel Agents, including Immune Therapies

DR. PAUL RICHARDSON:
Now this brings me really to my conclusion because we’ve got just a couple of more minutes before the hour. What I really wanted to share with you today was how innovations including the further refinement of proteasome inhibitors and IMiDs have produced really significant improvements.

What obviously, we have as a next wave of therapies primarily built around the immunotherapeutic platform that are showing great benefit, antibodies have primarily driven that. We now have, of course, exciting new HDACs, panobinostat being the approved one, AC241 on its way. I do want to emphasize, though, that we have BCL-2 inhibition with venetoclax, some beautiful data presenting at the meeting showing the benefit to this, particularly in combination with bortezomib. Also, want to mention that there was another very important class of drug, the so-called nuclear transport inhibitors or sign inhibitors, and in particular the data showing that this particular approach from the selinexor drug, which in combination with bortezomib, has shown dramatic effects. And the other – in the interest of time I wasn’t able to include slides on this – but there were beautiful presentations looking at selinexor both as a single agent and in combination with bortezomib, showing it to be very active, even in the setting of where all other treatments have failed. So, the kind of new small molecules that were the news of the meeting in terms of the ASH® 2016 meeting were venetoclax on the one hand, targeting BCL-1, and the nuclear transport inhibitor protein, selinexor, which also shows great results. So, real excitement around there. And then finally there were further refinements of prognostics and MRD that will guide therapy, that I think will help us.

SLIDE 89: Continuing Evolution of Multiple Myeloma Treatment: Selected New Classes and Targets 2016

So, in the context of how the landscape is looking from 2016 into 2017, you can see it summarized here. CAR-T cells, immunotherapy, exciting new small molecules. And I should mention for completeness there was some exciting data presented on a new proteasome inhibitor called marizomib, which is showing activity even in central nervous system and is very, very effective with pomalidomide. Interestingly, marizomib works very well when combined with pomalidomide. Already mentioned the next generation immunomodulators. And there is indeed a cytotoxic that’s a safer form or less toxic form of melphalan called melflufen, more targeted, where there are exciting data emerging. So, in addition to venetoclax, in addition to selinexor there are other drugs in the pipeline. So, a very exciting platform.

SLIDE 90: Ongoing MM Collaborative Model for Rapid Translation From Bench to Bedside

And this I think is the most important slide to share with you, which is that obviously 19 FDA approved drugs and combinations in the last 13 years, real progress. But I especially want to acknowledge the partnership that is part of that. And I especially want to acknowledge The LLS, which is part of this under advocacy. Also, the MMRF and IMF, and the other key agencies that make this possible, our pharma partners, the NIH (National Institutes of Health), the NCI (National Cancer Institute), and of course the FDA (Food and Drug Administration) and EMA (European Medicines Agency) that result in the progress that we’ve made.

SLIDE 91: The Impact of Novel Therapies in MM - 2016

And my last but final slide is actually the impact of novel therapies with a patient example. So, a wonderful patient of mine, is my privilege to care for, and she’s very happy to share her story and her picture. This is a picture of her at Cape Cod this summer. And as you can see, she was diagnosed in 2009, at the time was
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DR. PAUL RICHARDSON:
62 years old, and she had high risk myeloma. She had lots of features that would suggest that her disease would be very challenging to treat. Her only significant past medical history problem was hypertension. This was actually not trivial, she needed three drugs to control her blood pressure. She required RVD-based therapy to get into an excellent response. Fortunately, she tolerated this very well. She went on to a stem cell transplant. Unfortunately, that didn’t control her disease for very long, just one year, and then we were able to turn that around by adding bortezomib to her maintenance. Then she went on to pomalidomide-based therapy and did very well after that. But again, her disease blasted back because it was so aggressive. We did think about carfilzomib-based therapy, which would have been an excellent choice for her, but we stepped back from that because she had the high blood pressure issue and we know that for patients with high blood pressure carfilzomib can sometimes be challenging. So instead we used daratumumab and we used daratumumab as part of a clinical trial, the Phase I 501 study, she began this in 2013, and as you can see, for three years she’s been in complete remission on daratumumab as monotherapy, despite having very aggressive disease that unfortunately had grown through best IMiDs, best proteasome inhibitors and stem cell transplantation.

So, putting that altogether, it’s remarkable to have her at this stage in her illness in complete remission and feeling the best that she ever has since diagnosis.

So, I think this is an example of what these new treatments may offer our patients. And obviously recognizing every patient is different. This is what we think is really the hope for the future.

SLIDE 92: Thank You
And I want to close with my last and final slide, thank you so much for your kind attention. This is a smiling neutrophil, for those of you who may not be familiar with what a blood smear looks like, but this is actually a real picture from a patient’s peripheral blood and it was one that we couldn’t resist capturing. And my partner Dr. Phil McCarthy was so gracious to share this with me, I should say, to show you, because I think it summarizes how we feel about myeloma at the moment. Challenging it is, but the future is looking I think evermore hopeful.

Thank you very much for your kind attention.

SLIDE 93: Q&A Session
LIZETTE FIGUEROA-RIVERA:
Thank you so much, Dr. Richardson, for your very clear and thorough presentation.

And we’ll take our first question from our web audience. Doctor, David asks, should high risk smoldering myeloma continue to be monitored every other month or is there enough evidence to warrant entering a clinical trial? Would you recommend entering a clinical trial at this time?

DR. PAUL RICHARDSON:
In answer to the question, because it’s a very good question and it’s an excellent point, for patients with high risk smoldering myeloma we recommend careful observation and follow up as a standard. If they have evidence of bone thinning at all, we would recommend the use of a bisphosphonate because
DR. PAUL RICHARDSON:
there is clinical trial evidence that this may result in clinical benefit. And at the same time consideration of participation in clinical trials, particularly immunotherapeutic strategies, that include monoclonal antibodies, vaccines, for example, and the use of IMiDs. But off-protocol we cannot support off-protocol immunomodulatory treatment or other such approaches in the absence of participation in a clinical trial so far because really the evidence base remains very early.

Having said that, there is one randomized trial from Europe in which patients receive lenalidomide-based therapy and their survival benefit was shown. This requires further evaluation and validation, I think, because certainly whilst this trial was a breakthrough study, I think that the patient population studied in the United States certainly would be considered to have active myeloma. So, there’s a certain amount of caution. But suffice to say participation in clinical trials would be ideal, consideration of bisphosphonates would be perfect. There is randomized data to show benefit from lenalidomide, but again we would emphasize participation in clinical trials as probably the best way.

LIZETTE FIGUEROA-RIVERA:
Thank you, Doctor, and we’ll take the next question from our telephone audience, please.

OPERATOR:
Thank you. Our first question comes from Jane from Pennsylvania. Please state your question.

JANE:
Hi. I have multiple myeloma, I’ve had it since 2013. I was successful with the, I think the three-drug treatment, of going into remission. I had a stem cell transplant. The question I have is one of the drugs I was on was Revlimid® and after the stem cell transplant they put me on that as a maintenance drug and my system couldn’t tolerate it. So, my question is should I just wait until I get the disease again, it becomes active, or is there another drug that I should be taking now to keep me in remission?

DR. PAUL RICHARDSON:
That’s an excellent question and thank you so much for sharing it because it’s such an important thing. These questions are so helpful because obviously in the context of a presentation one can’t cover everything, so these questions are really useful.

So, for you I would say – how long have you been off Revlimid® now?

JANE:
August, 2013. So, three years.

DR. PAUL RICHARDSON:
What we know is that lenalidomide-based maintenance results in survival benefit and that’s been shown in a number of studies now. And most importantly in the most recent meta-analysis we showed that lenalidomide maintenance of some variety, however long you could tolerate it, resulted typically in a survival benefit of around two and a half years. So, with that information, the fact that there was an earnest attempt for you to receive lenalidomide – and how long did you get lenalidomide for?
JANE: Are you talking about Revlimid®?

DR. PAUL RICHARDSON: Yes, Revlimid®.

JANE: Okay, I had it for 18 weeks in 2013 and then I went into remission, so I had it then. And I took it for about two months after my stem cell transplant, but I had bad side effects, so they took me off of it.

DR. PAUL RICHARDSON: Yeah. So, the data currently show that for patients who – no matter how long you got it, for as long as you got it from the point of view of actually being able to tolerate it, you hopefully had gotten benefit. And the fact that you’ve been cancer-free now for three years since then points to that. Are you on a bone strengthener?

JANE: Yes, I get that every three months.

DR. PAUL RICHARDSON: Perfect. So, you should definitely stay on that because there is also now recent data to suggest that drugs like Zometa® and Aredia® have an immuno-oncologic effect. They have an effect on the immune system and bones. So, that’s relevant, that’s preclinical, so it remains early, but it’s very provocative. So, I think staying on the bisphosphonate is very important.

Now the interesting question is should you be on anything else. Well, the fact that you’ve been off-treatment for three years in addition, over and above the Zometa®, means that you’re probably in a very sustained remission and that’s good news for you. Really, we don’t know whether adding a maintenance drug now confers benefit, but what we do know is that in the setting of the randomized trials that we did, for those patients who were on placebo, and when the studies were closed because the benefit was shown to the maintenance and the placebo patients chose to go back onto a maintenance drug, we are seeing benefit to those patients. So, a discussion you might want to have with your local oncologist is there any rationale to me going back on some form of maintenance and if you did what might you use. Well, I’m trusting you probably got Velcade®, didn’t you, before your transplant, is that right?

JANE: That’s correct.

DR. PAUL RICHARDSON: How did you tolerate Velcade®?

JANE: It was okay. I had some side effects from all the chemo drugs combined. I think I tolerated it fine.
DR. PAUL RICHARDSON:
Yeah, because one question you might have for your oncologist is is there any rationale to just taking an occasional injection of Velcade®, typically every two weeks, as part of maintenance. Or there’s now been the introduction of ixazomib, which is this new pill form of Velcade® that can be given once a week and it’s approved after one line of therapy in patients with myeloma. So, there’s even a thought that adding, you know, once weekly ixazomib may not be unreasonable. Having said that, it may also be just as reasonable to sit tight, stay on Zometa® and see how you go. So, I think you have choices and I think my advice would be to discuss it with your oncologist and look at the pros and cons. But generally speaking, if you’ve been cancer-free for three years, despite a relatively short course of original lenalidomide, that’s obviously in itself very, very good news. Unfortunately, I can’t give you a definitive answer as to whether you should have maintenance added or not because unfortunately we don’t really know because you’re kind of unique in the way this has happened. But there are some suggestive lines of evidence that might suggest that you might benefit from the incorporation of something. Again, but I think that’s a discussion with your oncologist.

JANE:
Okay, thank you very much.

DR. PAUL RICHARDSON:
No, my pleasure.

LIZETTE FIGUEROA-RIVERA:
Thank you so much for the call and thank you, Dr. Richardson.

The next question comes from our web audience. Doctor, Doug asks, can a caregiver receive a shingles vaccine? I’m concerned about any shedding that may occur.

DR. PAUL RICHARDSON:
That’s a great question and certainly a caregiver can get the shingles vaccine. If there is any worry about shedding, it’s not unreasonable to put the patient on some acyclovir prophylaxis during the time that there may be shedding. That’s not an unreasonable strategy for the patient, so the caregiver can generate immunity without necessarily putting their loved one at risk. So, I think that’s a good question.

There have been studies now looking at the use of shingles vaccines for myeloma patients post-transplant and some of the early results from that suggested it’s a safe and feasible approach. But again, my own practice tends to stay away from vaccinating myeloma patients with shingles vaccines until we know more. I tend to rely on acyclovir or Valtrex being used.

A couple of practical points around that. Any patient after transplant should receive acyclovir prophylaxis for at least a year. Any patient receiving bortezomib, ixazomib or carfilzomib should receive acyclovir because the proteasome inhibitors always put a patient at slightly increased risk of shingles. And finally, patients getting daratumumab should be on acyclovir. And by extension, so they should if they’re getting isatuximab as well.
LIZETTE FIGUEROA-RIVERA:
Thank you, Doctor. And the next question comes from our web audience. Alexa asks, should foods high in protein be avoided as protein fuels cancer cells? My mom has begun drinking protein shakes for breakfast as a meal replacement and we wonder if it is therapeutic for her.

DR. PAUL RICHARDSON:
That's a great question and it's an often asked one and it's a very intelligent question actually because if you think about myeloma being a protein factory, wouldn't it make sense not to provide protein.

Well, actually the opposite is really true because there are good proteins and bad proteins, as I think most of us appreciate, and the good protein is what's called albumin and we need that for our immune system and for our red cells and white cells and platelets to work well, and all parts of our body to work well. So actually, a high protein diet is not an issue. You should have a good protein intake in one's diet.

The concept of what kind of diet matters is very interesting. We do know that myeloma – people who are obese are at an increased risk of myeloma, particularly in ladies. But now we know that that's true in men as well. So, obesity is associated with higher myeloma risk. So that perhaps gives us a clue that too much sugar, too much carbohydrate, too much fat may not be a good thing for myeloma patients. However, in terms of protein it's the opposite. I think chicken, fish, all the healthy types of proteins should be encouraged. And also, we believe strongly that a healthy diet really matters. This includes fruits, vegetables and particularly what I call the super veggies, you know, the cabbages, Brussels sprouts, broccolis, arugulas, kale, these kinds of things really matter.

Tangentially in other cancers we looked at things like multivitamins versus veggies. For example, my colleague Dr. Charles Fuchs led a beautiful study in colorectal cancer where he showed that if you take a multivitamin versus fruits and veggies, the multivitamin wasn't nearly as good as the fruits and veggies.

So, fruits and vegetables, healthy diet, olive oil, that kind of thing, all of these things we think matter. And indeed, a good healthy protein intake is probably as important as anything.

LIZETTE FIGUEROA-RIVERA:
Thank you, Doctor, and we'll take the next question from the telephone audience, please.

OPERATOR:
Thank you. Our next question comes from Dwight from Virginia. Please state your question.

DWIGHT:
Yes, thank you so much for this program today. I have been diagnosed with multiple myeloma since 2009. I've been through the various forms of the treatment. Did not elect to take the stem cell transplant because of age and lifestyle. But I have plateaued on Pomalyst® 2 milligrams in the 21-day cycle with a weekly 8 milligrams of dexamethasone and since November of 2013, the M-spike protein, which we measure monthly, has been at 0.1. I have never been in remission in the entire time, but I’m wondering with this plateau is there anything further to be gained beyond simply waiting until the next stage or is there something that I maybe should discuss with my oncologist at this point?
DR. PAUL RICHARDSON:
That’s an absolutely super question, sir, and if I may, I apologize, I didn’t quite hear clearly what you’d had initially, what was your initial treatment?

DWIGHT:
My initial treatment was the thalidomide, the bone strengthener, and I took that, and then with Revlimid®, which I did not do very well, and then Velcade®, both the IV and then the injection, and in November of 2013 went to Pomalyst®.

DR. PAUL RICHARDSON:
Excellent. And you’re on pomalidomide right now, sir, correct?

DWIGHT:
Yes, since 2013.

DR. PAUL RICHARDSON:
I’m delighted to hear and well done. Have you ever had a stem cell transplant, sir?

DWIGHT:
No, I did not elect to take – I was worked up for that initially and approved, but elected not to go that route.

DR. PAUL RICHARDSON:
These questions are so helpful because they bring out so many principles around the management of the disease.

The transplant data that was presented at ASH® suggested that whilst transplant could result in a progression-free survival advantage if it was used early versus late, there was no benefit in overall survival. And what that tells us I think is that transplant is a useful tool in selected patients, but it’s truly not a case of one size fits all. And especially in the United States we’re lucky enough, because we have so many other treatment options, that we can afford to perhaps keep it in reserve if we need to. So the fact you chose not to pursue a transplant right away I think is perfectly reasonable, and how you’ve done sort of reflects that. Can you remind me, sir, how long ago were you first diagnosed?

DWIGHT:
2009.

DR. PAUL RICHARDSON:
Lovely, so you’ve been diagnosed seven years. And how old were you then and how old are you now?

DWIGHT:
71 now and we can back up from there, 64.
DR. PAUL RICHARDSON:
63, 64, good for you. I think going forward, and you haven’t had stem cells collected, correct?

DWIGHT: No, sir.

DR. PAUL RICHARDSON:
No. And that’s okay, too, because what we’re realizing is that whilst collecting stem cells early is ideal if the resources are there and it’s easy to do, particularly if you’re substantially younger, if you don’t it’s not the end of the world, you can easily mobilize stem cells later as well in fact, especially with some of the newer mobilization strategies, such as what we call plerixafor.

In any event, right now you’ve done very well, good for you. Pomalyst® is suiting you well, sir, is it giving you any side effects or not?

DWIGHT: Not really, no.

DR. PAUL RICHARDSON:
Good. And it’s very interesting, this is why we need all the IMiDs, because you did well with thalidomide clearly. Unfortunately, Revlimid® was a little difficult for you. But isn’t it interesting that pomalidomide worked well for you because they’re subtly different drugs, but look at how the difference it’s made for you. You’re tolerating pomalidomide much better and I must say I have a number of patients in whom lenalidomide hasn’t worked as well as we would have liked and we found pomalidomide to really suit them well. So, that’s an interesting point as well.

So, in terms of the future, right now you’ve got a little residual protein. You can stay on the pomalidomide, that’s essential, you mustn’t not do the pomalidomide. If you wanted to get a deeper response there might be a rationale for adding something like elotuzumab, the antibody, which is very well tolerated. You might even add bortezomib because that can enhance pomalidomide dramatically. How did you get on with the bortezomib when you had it?

DWIGHT: Very good. In fact, I thought I was going to be the bortezomib poster boy.

DR. PAUL RICHARDSON:
Well, the good news is that some patients do extremely well with bortezomib. The biggest challenge with bortezomib is neuropathy, of course, and we work very hard to improve that by using various strategies. Do you have any neuropathy at all?

DWIGHT: I do have some, but you know, it’s tolerated, let’s put it that way.
DR. PAUL RICHARDSON:
Right. So, the other option of course is ixazomib, which is the pill form of Velcade®. It’s different to Velcade®
actually, so it’s not fair to say it’s the pill form. It’s a different drug, but it’s in the same class.

DWIGHT:
Can that be added?

DR. PAUL RICHARDSON:
Well, that’s an interesting question and the question really is do you need to. And this is the critical point.
We do believe, generally speaking, that complete remission matters, and we do believe that being quote-
unquote MRD negative, certainly in the research area, is an important surrogate for improving outcome.
What’s so complicated in myeloma, though, is that there are a subset of patients in whom residual protein,
they can have for many years and they do very, very well. And there are some folks who achieve complete
remission, everything disappears and you think, God, we’re home and dry, and then suddenly bang out of
the blue, myeloma comes roaring back. So, it’s always a bit of a judgment call, to be honest, sir.

I think personally that right now you’re doing very well on pomalidomide. Are you taking any steroid with it?

DWIGHT:
I’m taking weekly dexamethasone 8 milligrams once a week.

DR. PAUL RICHARDSON:
And how are you tolerating that?

DWIGHT:
It winds me up like a clock.

DR. PAUL RICHARDSON:
Yeah, that’s the challenge, that’s the challenge. You might want to talk to your oncologist about dialing down
the steroid, so taking it down from 8 to 4, and perhaps thinking about adding something to the cocktail. One
thing you could do is add Velcade® every two weeks. That might do you no harm at all, from the neuropathy
point of view, and might allow you to use less steroid and actually get a deeper remission from your
Pomalyst®. What dose of pomalidomide are you on?

DWIGHT:
2 milligrams.

DR. PAUL RICHARDSON:
Perfect. The other option would be to think about elotuzumab. The problem with that is it’s a more frequent
administration, because it’s weekly initially and then every two weeks and then every month. Also in
fairness, your insurance company might say it’s not approved for that, so that might be a bit of a challenge.
But Velcade® would be an easy one. The other one would be ixazomib, which is this pill once a week. Those
might be strategies that would allow you to use less steroid and enhance the effect of the
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Speaker: Paul G. Richardson, MD

DR. PAUL RICHARDSON:
pomalidomide and get you into the complete remission that might make you feel more comfortable and your doctor feel more comfortable.

But I think the important message, and it’s a great one to share with the audience, is that complete remission does matter, but it’s not the be-end and end-all in every patient. And in fact, I have patients of mine who’ve lived with their myeloma ten, twelve years with residual protein and they do very, very well. So, it’s always a question of the nuances and the judgments around risk and benefit that need to be factored in. But I think it’d be very reasonable for you to talk about adding bortezomib or ixazomib to your doctor or elotuzumab if that was feasible. Remembering, sir, that you have in reserve for you drugs like daratumumab, carfilzomib if you don’t have any cardiovascular risk or anything like that, and other drugs as well, ready for you if you need them in the future.

And it’s great to hear that you’re now seven years into your illness because, you know, God willing, you will enjoy many, many more years of disease control and the very, very best to you.

DWIGHT:
Thank you, thank you so much.

DR. PAUL RICHARDSON:
Pleasure.

LIZETTE FIGUEROA-RIVERA:
Thank you. And you did mention neuropathy, Doctor. Edward was asking about managing side effects such as neuropathy and severe bone pain.

DR. PAUL RICHARDSON:
Neuropathy can be a real challenge and I think that this is an important side effect issue to touch on. With bortezomib, the administration of bortezomib under the skin, so-called subco, can dramatically reduce neuropathy. Dose reduction and less frequent administration of bortezomib is critical in minimizing the side effect. And the use of intravenous hydration we think really matters, as does the use of emollient creams and supplements to minimize neurotoxicity. So all of these things should be discussed with your oncologist and sort out to manage bortezomib neuropathy.

Same principles apply to the neuropathy of pomalidomide and thalidomide. The good news is that with Revlimid, or lenalidomide, neuropathy is less common, but still occurs in a low grade, in a few patients. So, it’s worth remembering.

For patients on lenalidomide muscle cramping can be an issue. So, the use of therapeutic massage, the use of supplements, especially calcium, magnesium and potassium, can be very helpful in reducing the muscle cramping associated with lenalidomide use.

Bortezomib, in addition to being given subcutaneously, reduced frequency and so on, a critical aspect to managing neuropathy from either bortezomib or any of the drugs we use, is the use of certain drugs like gabapentin, Lyrica®, and also drugs like Celexa®, which can be very useful in terms of minimizing neuropathic pain.
DR. PAUL RICHARDSON:
The good news about neuropathy is it’s very, very rarely life-threatening, that’s the critical point. The challenge is it’s a real nuisance. And so working hard to prevent it and minimize it is critical.

In that same context, the use of non-neurotoxic drugs like carfilzomib has been a real breakthrough. The challenge is that no drug in myeloma has no side effects, unfortunately, and with carfilzomib, whilst most people tolerate it very well, there are a subset of patients who get into trouble with blood clots, high blood pressure, lung difficulties and heart trouble. And we’re trying to figure out why they do that and kind of protect them from it. But that’s an ongoing area of research.

LIZETTE FIGUEROA-RIVERA:
Thank you, Doctor. And our next question does come from the web. Barry asks, what studies are there for non-secretory disease and what progress has been made in this area?

DR. PAUL RICHARDSON:
That’s a very interesting question about non-secretory disease. I would suggest that we can look at a variety of – sorry, basically non-secretory disease is a challenge. It’s not as common as – sorry, it’s not as rare as people – let me flip that around. The true non-secretory disease is extremely rare. The reason why is because what we’re realized is that you can usually track it with free light measurements, for example, and obviously, the advent of PET-CT scanning has been a real bonus because it’s allowed us to image in a way that has made this a much more viable or rather measurable disease.

So, in terms of research around it, typically non-secretory disease likes to be extramedullary, it likes to spread to non-marrow sites, be lumpy, bumpy in its nature. The good news is the antibodies particularly like to go after it, so drugs like daratumumab are very effective. We’ve found also that non-secretory disease, because it’s more difficult to follow, can sometimes be associated with somewhat worse outcomes. Now with the newer drugs we’re seeing that they, non-secretory patients, can do very well in the long term. So it’s being studied in the sense that we’re applying other technologies to it, being able to measure and assess it better, and so be able to treat it better in that same context.

LIZETTE FIGUEROA-RIVERA:
Thank you. And Linda asks, our last question, she’s asking are myeloma vaccines on the horizon?

DR. PAUL RICHARDSON:
They most certainly are on the horizon. They are basically something we want to use in the minimal disease setting ideally because they not only require the immune system to be able to be as functional as possible when we use them, but at the same time we want to try and generate memory, which means that the immune system can then memorize the characterization of the disease, and so help keep the disease under control for longer.

I think they’re particularly exciting in the smoldering or early stage phase because that’s when the immune system is most robust. I also think they’re very exciting post-transplant or post-induction remission therapy, so there are a number of vaccine studies currently underway, both post-transplant and in smoldering disease that I think are very promising, particularly if you combine them with checkpoint inhibitors and antibodies and IMiDs in particular.
DR. PAUL RICHARDSON:
So, vaccines I would say watch this space, it’s very exciting. But can they be effective in very advanced disease? That’s a very challenging area. There was, as you know, some excitement around the measles virus – measles vaccine I should say. The fact is that some of that turned out not to quite turn out as reproducible as was originally thought. But we’re obviously continuing to pursue other avenues that are also very promising.

LIZETTE FIGUEROA-RIVERA:
Thank you so much, Dr. Richardson, for your continued dedication to patients and, of course, for volunteering your time with us today.

For those of you who participated in today’s program we hope the information presented today will assist you and your family in your next steps.

If we weren’t able to get to your question today, you can call The Leukemia & Lymphoma Society’s Information Specialists at 1-800-955-4572 from 9 AM to 9 PM Eastern Time, Monday through Friday, or reach us by email at infocenter@LLS.org. Information Specialists are available to answer your questions about treatment, including clinical trials, or answer other questions you may have about support, including financial assistance for treatment.

Again, we would like to thank Amgen Inc., Bristol-Myers Squibb, Celgene Corporation, Sanofi US, and Takeda Oncology for their support for this program.

Dr. Richardson, thanks again for volunteering your time with us today, and on behalf of The Leukemia & Lymphoma Society, thank you all for joining us. Goodbye and we wish you well.