Myeloma – Update on Research and Treatment from the American Society of Hematology (ASH®) Annual Meeting

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January 21, 2014 | **Speaker:** Robert Z. Orlowski, PhD, MD

Slide 1 - Welcome & Introductions

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

LAUREN BERGER:
Thank you and hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Special thanks to Dr. Robert Orlowski for sharing his time and expertise with us today. Following the presentation, we'll take questions from the audience. Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's President and CEO, John Walter, who will share a few words. John, please go ahead.

JOHN WALTER:
Thank you, Lauren. I'd like to add my welcome to the patients, caregivers, and healthcare professionals on the program today.

The Leukemia & Lymphoma Society exists to find cures and ensure access to treatments for blood cancer patients. We have one goal: a world without blood cancer.

For more than 60 years, LLS has helped pioneer innovations such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients.

To date we have invested nearly $1 billion in research to advance therapies and save lives.

Until there is a cure, LLS will continue to fund promising research from bench to bedside.

LLS is a voice for all blood cancer patients. We are the leading source of free blood cancer information, education and support, and we touch patients in their communities through our 61 chapters in the United States and Canada.

We advocate for blood cancer patient survivors and their families, helping them navigate their cancer treatments, and ensuring they have access to quality, affordable and coordinated care.

We are fortunate to have as our presenter today Dr. Robert Orlowski, one of the nation's leading experts in myeloma. We appreciate his dedication to supporting our mission and commitment to caring for patients living with blood cancers. I'd like to thank him for providing us today with important information about myeloma.

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

Slide 2 – Title Slide

LAUREN BERGER:
Thanks, John.

LAUREN BERGER:
I am now pleased to introduce Dr. Robert Orlowski, Florence Maude Thomas Cancer Research Professor, Director of the Myeloma Section, Departments of Lymphoma, Myeloma and Experimental Therapeutics in the Division of Cancer Medicine at the University of Texas M. D. Anderson Cancer Center in Houston, Texas.

On behalf of The Leukemia & Lymphoma Society, thank you so much for volunteering your time and expertise today. Dr. Orlowski, I am now privileged to turn the program over to you.

Slide 3 – Outline - Disease Biology

DR. ROBERT ORLOWSKI:
I would also like to especially thank Lauren and John and the whole team at The Leukemia & Lymphoma Society for putting this program together, and for everything that the Society does, including supporting cutting edge research in hematologic malignancies as well as in directly supporting patients, which is something that most people don't know about. And one particular point that we should make, which many people don't know, is that The Leukemia & Lymphoma Society supported the first clinical trial that showed the activity of bortezomib against myeloma, which of course has become one of the standards of care in this disease. Therefore, Leukemia & Lymphoma Society has really made a difference.

I'm going to cover a few different topics, which will range from disease biology, new molecular information, as well as various categories of myeloma including asymptomatic myeloma, treatment for patients that are not transplant candidates or that are, options for treatment around the time of transplant, then what we can do in the relapsed or refractory setting, and eventually talk about some aspects of supportive care. And I'm going to cover the material that are in your slides, but because of time constraints I'm not going to be able to cover all of the material, but I thought I would give you more than what I could talk about, so that this could serve as a useful reference.

Slide 4 – 2013 ASH Abstract 529
First on the topic of disease biology, one of the more important things, especially for newly diagnosed, but also for patients with relapsed disease, is to try to get an idea of whether their disease is high risk or standard risk because there is an emerging understanding that those two different categories should be treated differently.

Slide 5 – Hyperdiploidy +/- Other Lesions
One of the ways in which this is determined is by looking at cytogenetics, by routine karyotyping of the bone marrow. Sometimes patients will have a good risk abnormality and one example of that is hyperdiploidy. What that means is that there is more than the usual number of chromosomes present in the myeloma cell. Other people will also on top of that have a bad risk prognostic feature, and examples of that include deletion of chromosome 17p or additional material at 1q.

The current abstract that is on your slide is asking the question when you have patients with both a good risk feature and a not so good risk feature, what does that mean? Does that mean they're good risk, intermediate or bad risk? And unfortunately here it looks like the answer is, if you look at, for example, hyperdiploidy or HD, plus deletion of 17p, you can see that the overall survival in those patients is significantly worse than is the case for hyperdiploidy without an adverse abnormality. And the same thing

DR. ROBERT ORLOWSKI:
is true with the 1q plus mutation. And if patients have more than one high risk feature, their overall survival goes down even further.

So I think it's important therefore for you to know not just that you have multiple myeloma, but what type you have, because probably different treatments would be warranted if you're good risk or high risk.

Slide 6 – 2013 ASH Abstract 689
Despite the fact that these data would suggest that deletion of 17p is a poor risk feature, which in fact it is, and it can be present in about 10% of newly diagnosed patients, and up to 30% of patients with relapsed disease, there is some good news in that area.

Slide 7 – Pomalidomide and Deletion 17p
For example, there was this abstract, number 689, which looked at the effect of pomalidomide with low dose dexamethasone for patients with this high risk chromosome abnormality. You may know that pomalidomide and dexamethasone was just approved last year for relapsed and refractory disease. In this study, which was led by the French Myeloma Group, they looked at outcomes for patients that had this deletion of 17p. You can see in this curve that time to progression was actually better for patients with deletion 17p who got pomalidomide and dexamethasone. Therefore, for those of you that may have deletion 17p among the abnormalities in your myeloma cells, data like this argue that pomalidomide may be a very good drug to consider for treatment.

Slide 8 – 2013 ASH Abstract 123
Finally, in the disease biology category, one of the things that we don't yet have in myeloma is the ability to predict ahead of time which patients will respond to which treatment, because we don't have what are called biomarkers. Recently with the immunomodulatory drugs like thalidomide, lenalidomide and pomalidomide, there is a feeling that perhaps there is a gene called Cereblon whose expression may predict response in advance, although studies still need to be done to validate that.

Slide 9 – TJP1 Sensitizes to Bortezomib
In this abstract, which was number 123, and these were data actually from our group at MD Anderson, we were able to show that another gene called TJP1 or Tight Junction Protein 1, may be predictive for a response to proteasome inhibitor-based therapy. The data in the slide show that if you have high expression of TJP1, your benefit from bortezomib or bortezomib-based combinations was much greater than was the case if you had low TJP1 expression. In the table, you'll see that median time to progression was about 90 days if you had low levels versus 180 days if you had high levels of TJP1. Even the 90 days may be a reasonable target to go after, but we also think that there will be ways that we can improve upon that based on the understanding of how this gene influences sensitivity in myeloma.

So like Cereblon, we need additional validation, but I think the take-home message here is that we are learning more about myeloma biology and hopefully soon we'll be at the point where we can predict ahead of time what combinations will work best in which patients, which will improve outcomes and reduce side effects.

DR. ROBERT ORLOWSKI:

Slide 10 – Outline - Asymptomatic Myeloma
I'd now like to move over to asymptomatic myeloma, which also is known as smoldering myeloma.

Slide 11 – 2013 ASH Abstract 1939
This is an area where there's been a lot of excitement because of recent data that suggest that high risk smoldering patients may benefit from starting therapy early, as opposed to the current standard, which is watch and wait.

Slide 12 – Study Design
One of the abstracts at ASH which looked at this was abstract 1939. What they did in this particular trial, which was done by Ola Landgren at the NIH, is they looked at a combination of carfilzomib, lenalidomide and dexamethasone as an initial therapy, followed by extended dosing with lenalidomide for these patients with high risk disease.

Slide 13 – Response Rate and Quality
What they found in a relatively small patient population, so I think we have to be a little bit cautious in interpreting this, but they did excitingly find that 100% of these patients had a response and almost all of them had a complete remission. On the right you can see that almost all of them had a molecular remission as well. This was based on using flow cytometry to look at each plasma cell in the patient's bone marrow aspirate sample.

Slide 14 – Toxicities
This approach was not without side effects because there were some problems with liver test elevations and electrolyte disturbances and there could be issues in a few patients with kidney damage or heart damage. But data like this are very encouraging, because when we start seeing molecular remission, we all get excited about the possibility of cure. These data do suggest that especially high risk patients with so-called smoldering or asymptomatic myeloma should look for clinical trial opportunities with some of these novel approaches. Hopefully one or another of these will show us in the future that we can maybe even prevent the outbreak of symptomatic myeloma.

Slide 15 – Outline - Non-transplant Therapies
I'd now like to move to some of the developments that have occurred for patients who are not transplant candidates at the time that they're diagnosed, which is usually because of other medical problems. For example, poor heart or lung or kidney function, or in some cases because of older physiologic age. Not chronologic age, by the way.

Slide 16 – 2013 ASH Abstract 2
In this category there were a number of important developments. One of those is the so-called FIRST Trial, and this was part of the ASH plenary session. The plenary session selects out what were felt to be the most important abstracts in the entire meeting for presentation at a large session, and this myeloma abstract made the cut. Actually this was the largest myeloma study that has ever been conducted to date so far in a clinical trial.

DR. ROBERT ORLOWSKI:

Slide 17 – Study Design
They randomized transplant ineligible patients to receive one of three treatments. Either they got melphalan, prednisone and thalidomide, or they got lenalidomide with low dose dexamethasone. Those two arms were continued for 72 weeks and then stopped. The third arm, which was arm A, did lenalidomide and low dose dexamethasone continuously, without stopping, until there was either some side effect or disease progression.

Slide 18 – Progression-free Survival
In terms of progression-free survival, the curves shown here show you that the patients that did the best were those that got lenalidomide and dexamethasone until progression. Their disease tended to stay in remission for a longer period of time than those patients who did 72 weeks of treatment and then stopped.

Slide 19 – Forest Plot of Subgroups
When you look at some of the different groups that benefitted, it looks like virtually all patients with myeloma did better with lenalidomide and dex than they did with melphalan, prednisone and thalidomide. The two exceptions, which are circled, are patients who have high LDH or lactate dehydrogenase, who are those who had high risk cytogenetic features. Those high risk features may do better with different drugs. For example, maybe pomalidomide and dexamethasone as we talked about earlier. But still, almost everybody did better with lenalidomide and dexamethasone.

Slide 20 – Interim Analysis of Overall Survival
Here is the plot of the overall survival. Although the curves are close together, there is a significant benefit for those patients who got lenalidomide and dexamethasone, compared to melphalan, prednisone and thalidomide.

So that really establishes lenalidomide and dex as a standard of care for patients who are not transplant candidates as initial therapy, and also says that treatment should be continued until progression.

One other important feature here is that there was not apparently an increased risk of second cancers, which has been a concern with lenalidomide before. Actually the melphalan, prednisone and thalidomide arm in this study had more second cancers, so this approach also had a nice safety profile.

Slide 21 – 2013 ASH Abstract 536
Another study that was interesting in this regard was an update of a trial that looked at melphalan, prednisone and lenalidomide, or cyclophosphamide, prednisone and lenalidomide, after lenalidomide and dexamethasone.

Slide 22 – Study Design
Here you can see the three different arms. One was LEN-DEX, which was as was in the previous study. A second arm was melphalan, prednisone, lenalidomide, and a third arm was cyclophosphamide with lenalidomide and prednisone.

DR. ROBERT ORLOWSKI:

Slide 23 – Patient Outcomes
These investigators found that progression-free survival and overall survival were pretty similar for the three. This argues that lenalidomide and dexamethasone is probably better because any time you can use two drugs as opposed to three drugs, you're probably going to have fewer side effects, which is always an important endpoint.

Slide 24 – 2013 ASH Abstract 405
One update of a study that I think is worth mentioning was this update from the MM-015 trial, which was abstract 405.

Slide 25 – Emerging Concept: PFS2
This study looked at melphalan, prednisone and lenalidomide, followed by lenalidomide maintenance. The other arms were melphalan and prednisone or MPR without lenalidomide maintenance.

One of the concerns that we've always had is that if we continue maintenance for a long period of time, when the myeloma does relapse, it may be more aggressive, less responsive to treatment, and therefore we may actually do a disservice to patients by maintenance therapy. But if you look at the bottom of this table, where you see PFS2, those are data that show time to progression on the next treatment after progression on initial therapy. What you can see is that the group that got MPR followed by lenalidomide maintenance had actually a better second progression-free survival than did the patients who got just melphalan and prednisone. This suggests that in fact maintenance does not cause more aggressive disease to grow out and that the better treatment up front also results in better benefits at the time of relapse.

Slide 26 – 2013 ASH Abstract 685
Another study, to briefly talk about, was this one, number 685, which looked at carfilzomib with cyclophosphamide and dexamethasone.

Slide 27 – 2013 ASH Abstract 685
Some of you may have already gotten treatment with a combination that's been very similar, which is bortezomib with cyclophosphamide and dexamethasone, or CyBorD. In this study what was done was that instead of bortezomib, carfilzomib was used on a pretty standard schedule.

Slide 28 – Response Timecourse
The response rate was in the 85 to 95 percent range, and the durability of this was quite good. So this could also be considered an option for treatment of patients that are not eligible for stem cell transplant, and also even for transplant-eligible patients.

Slide 29 – Outline - Induction Before Transplant
With the eligible patient population in mind, let's look at a few of the studies that examined different types of treatment prior to possible stem cell transplant.

DR. ROBERT ORLOWSKI:

Slide 30 – 2013 ASH Abstract 688
One of these looked at carfilzomib with thalidomide and dexamethasone.

Slide 31 – Study Design
I think the interesting thing about this study is that in addition to the initial induction therapy, which was later followed by stem cell transplant, they also gave consolidation chemotherapy after the transplant, with the same combination as was used in induction. More and more people are now going to this consolidation approach with the idea being that, especially if there is some myeloma left after transplant, going after it with a more aggressive therapy for one or two or in this case four cycles before doing maintenance, can result in a potential benefit.

Slide 32 – Response Data
You can see from the response data here that with just the induction alone 93% of patients had at least a partial remission, but only 17% of patients had a complete remission. Then when you added transplant, that went up to 31%, and then when you added the consolidation, that went up to 51%. This really suggests that adding some consolidation, especially if you're not in complete remission after transplant, can be of benefit.

Slide 33 – Long-term Outcomes
It's also important to note that if you're not in complete remission, that doesn't necessarily mean the end of the world, since many patients who are close to complete remission can do very well. So just because you're not in CR doesn't mean you need more treatment. That's an area that you should really talk to your myeloma specialist about before you commit to doing more therapy. This slide shows you that the long-term outcomes with that combination were quite good.

Slide 34 – 2013 ASH Abstract 535
Another up-front therapy that may be in use in the near future is an all-oral combination.

Slide 35 – Study Design
The previous combinations that we reviewed, including carfilzomib, do involve some intravenous treatment. But there is now an oral proteasome inhibitor. It's called ixazomib or MLN9708. In this study, number 535 from Paul Richardson and his colleagues, they looked at combining lenalidomide and dexamethasone with this oral proteasome inhibitor as an initial therapy. They gave the oral proteasome inhibitor twice a week, but there also are studies ongoing where this is given once per week.

Slide 36 – Response Data
The exciting data here are shown with a response rate of 93 to 95%, and a large proportion of patients having a complete remission or a very good partial remission. This is going to be more convenient because all of the medications are oral. The one downside is that with the twice a week dosing of this oral inhibitor, you do have a little bit more episodes of rash, but the once a week dosing is very well tolerated. There is a clinical trial ongoing for newly diagnosed patients, comparing lenalidomide and dex with this three drug all-oral combination. So hopefully some of you may be able to access this study and participate in this trial.

DR. ROBERT ORLOWSKI:

Slide 37 – 2013 ASH Abstract 538
Another combination that has gotten very good response rates in this setting is carfilzomib with lenalidomide and dexamethasone.

Slide 38 – Study Design
This abstract, number 538, was an update of a trial from the National Cancer Institute. The design was similar to what was used for the smoldering study that we reviewed earlier.

Slide 39 – Response Data
You can see that again here the response rates were very high. Almost 100% of patients had a partial remission or better, and two-thirds of patients had a complete response or better, while many patients were in molecular remission. So it will be interesting to see how the long-term outcomes turn out. By the way, there is an ongoing study through the Cooperative Group mechanism, meaning that it should be available at virtually every institution around the country, which is comparing this regimen, CRD versus VRD, to see which one has the better response rate and durability. Hopefully some of you will be able to access that.

Slide 40 – Outline - Options for Therapy After Transplant
Now once you do get stem cell transplant, is there some additional therapy that you should get, and we've talked a little bit about maintenance.

Slide 41 – 2013 ASH Abstract 763
But some of the work that was presented looked at other options.

Slide 42 – Study Design
One trial, which was this one, number 763, was interesting. It actually asked a slightly different question, as you can see here. All patients got lenalidomide and dexamethasone to begin with, but then they were randomized first either to transplant or consolidation with chemotherapy. After that all of the patients were randomized either to lenalidomide maintenance or to lenalidomide with prednisone. Many of my patients when I see them in clinic say, you've got all of these new drugs, could I just get a combination of new drugs and not do the stem cell transplant, or is it still important for me to do that?

Slide 43 – Primary Analysis
If you look at the data in the primary analysis and you look at progression-free survival, what you can see is that the yellow curve, which were the patients who got melphalan or stem cell transplant, did better than the patients who got the chemotherapy-only approach. Although on the right you'll see that overall survival was not yet different. Oftentimes in terms of overall survival these studies can take many years before the data mature. But usually a progression-free survival difference translates into an overall survival difference.

So this would lead me to suggest that in fact transplant is still important, even though we have all of these new drugs that we can use.

DR. ROBERT ORLOWSKI:

Slide 44 – Landmark Analysis
Then also there was analysis looking at whether the LEN by itself or the lenalidomide with prednisone was the better maintenance. The early data on the left suggest that maybe the combination is better, although for right now I still think that lenalidomide alone is the standard of care.

Slide 45 – 2013 ASH Abstract 406
One of the studies that established that LEN maintenance is the standard of care was this IFM Trial in abstract 406. Some of you may know that this was published in the New England Journal of Medicine.

Slide 46 – Study Design
This study took patients after transplant, gave all of them two months of lenalidomide consolidation, and then randomized them either to more lenalidomide or to placebo.

Slide 47 – Analysis After Relapse
Earlier analyses had shown that progression-free survival was better for lenalidomide, but overall survival was not different. So in this analysis the French investigators tried to answer the question, which we talked about a little bit earlier, i.e. what happens once patients do relapse? This was a very hotly contested abstract, and the reason is that the data shown here suggested that the patients who got lenalidomide maintenance actually did worse with whatever was their second-line treatment once they progressed on maintenance. That's a concern because it gets back to the question I mentioned earlier about maybe drug resistance being an issue.

Slide 48 – Treatment After Relapse
However, when you look at the treatment that they got, it turns out that everything depended on what they received as their second-line treatment. If they progressed on lenalidomide and then got another drug in the same class, as you can see on the left, they did poorly. But if they got a bortezomib-based therapy on the right, they did well.

So I think really the lesson here is not that lenalidomide maintenance causes drug resistance. The lesson here is that it is important what sequence of treatments you use and you should try to alternate between an immunomodulatory drug and a proteasome inhibitor-based combination.

Slide 49 – 2013 ASH Abstract 407
To further look at whether maintenance lenalidomide is an important way to go, a meta-analysis was done by these investigators, abstract number 407.

Slide 50 – Analysis After Relapse
In a meta-analysis, statisticians take the data from different clinical trials, combine them, and try to come up with a conclusion. In this study, the conclusion they came up with is that there was enough data to favor lenalidomide versus no maintenance as a treatment for myeloma after transplant.

You can see that the red diamond in the figure is to the left and therefore favors lenalidomide. Therefore, I do think, as I've mentioned before, that LEN maintenance after transplant is still a standard of care.

DR. ROBERT ORLOWSKI:

Slide 51 – 2013 ASH Abstract 404
One other approach that we could consider is to use bortezomib as a maintenance, and one study that did that was this trial from the Dutch and the Germans.

Slide 52 – Study Design
The design of this is that patients either got VAD, transplant and thalidomide maintenance – VAD is an older treatment with vincristine, doxorubicin and DEX – and the other group got PAD, which is bortezomib, doxorubicin and DEX – followed by transplant, followed by maintenance with bortezomib.

Slide 53 – Starting with Maintenance
In the analysis, looking at what happened after maintenance, if you look on the right, it looks like the patients who got bortezomib maintenance were doing better than those who got thalidomide maintenance.

Bortezomib is not the most convenient treatment for maintenance because it is still an injection, but at MD Anderson we're running a trial with the MLN9708 oral proteasome inhibitor for maintenance in combination with lenalidomide. So far that's looking exciting and would be a great way to go because it would be an all-oral approach to maintenance therapy.

Slide 54 – Outline - Relapsed and/or Refractory Myeloma
Despite all of these great treatment options up front, patients are still unfortunately developing disease that has relapsed or in some cases is refractory.

Slide 55 – 2013 ASH Abstract 283
There was good news from ASH about a number of new drugs. One is this AKT inhibitor, presented in abstract 283.

Slide 56 – Analysis After Relapse
AKT is a gene and protein which is important to myeloma cell survival, and if you block it, myeloma cells tend to die.

This study, led by Peter Voorhees at UNC in Chapel Hill, showed that this three drug combination had an overall response rate that was as high as 73%, including some patients with complete and even stringent complete remission.

Slide 57 – Activity by Prior Bortezomib Exposure
In particular, if you look at those patients who were bortezomib-exposed or bortezomib-refractory because their disease grew through bortezomib, up to 43% of those responded to this combination. That's an exciting number and hopefully this drug will be available in larger clinical trials in the future.

Slide 58 – 2013 ASH Abstract 284
Another drug that I would say made a bit of a splash is a drug that doesn't yet have a name. It has only a letter and number designation, SAR650984. This is an antibody that attaches to a protein called CD38, a protein that is expressed on almost all myeloma cells.

DR. ROBERT ORLOWSKI:

Slide 59 – Response Data
In this study they did an evaluation of this drug and you can see that patients had complete responses, partial responses and minor responses, with a response rate of about 31%, which is encouraging for a single agent. Nothing else was given here, and probably if you combined it with bortezomib or lenalidomide, the response rate will be even higher. We're looking forward to combinations with this drug as well.

Slide 60 – 2013 ASH Abstract 1986
There's another antibody against CD38 that some of you may have heard of, it's called daratumumab, which was given a breakthrough therapy designation by the FDA. The exciting thing is that these two drugs, even though they both go after the same target, attach to different parts of CD38, which means that it may be possible to use them either sequentially, one after another, or maybe even in combination in the future, although we don't have those data yet.

Data were presented at ASH with the combination of daratumumab with lenalidomide and dexamethasone.

Slide 61 – Response Data
You can see that the response data showed high numbers of responders in this group, though this is still a small trial, so we don't have as much information as we'd like. There is a Phase III study which is being planned, which will be lenalidomide and dex versus daratumumab, lenalidomide and dex for patients with one or more prior therapies.

Slide 62 – Adverse Events
If you look at some of the side effects, this is generally a very well tolerated drug, although it does have some infusion-related reactions, which can be taken care of quite nicely.

Slide 63 – 2013 ASH Abstract 690
One option for relapsed or refractory disease, which is important to keep in mind, is this combination of carfilzomib with pomalidomide and dexamethasone. This was a trial led by an investigator at MD Anderson, Dr. Jatin Shah.

Slide 64 – Response Data/Long-term Outcomes
What we found in this combination is that the response rate was up to 83%. These were all patients whose disease was refractory to lenalidomide. The reason this is important is that because both of these drugs are already FDA approved, although we'd love for you to come to MD Anderson and be on this trial, your doctor at home can actually give this combination. When all of the drugs are approved, you can combine them in any way that you like, so this is a regimen that you can receive at home. Also, if you look again at the curves at the bottom, which look at this high risk deletion 17p abnormality, you can see that patients with this high risk disease did quite well, so if you've got deletion 17p, think about this combination as a treatment.

DR. ROBERT ORLOWSKI:

Slide 65 – 2013 ASH Abstract 285
The one other new drug that I thought I would mention because it will be available in clinical trials for patients with relapsed or refractory disease, is a drug which back then still had just a letter and number designation, ARRY-520. Now it actually has a name, so it's graduated to that level, and the name is filanesib.

Slide 66 – Mechanism of Action
This is a drug which works by preventing myeloma cells from dividing, by attacking a target called KSP, or kinesin spindle protein.

Slide 67 – Study Design
Many of you, unfortunately, are probably suffering from some level of neuropathy because of a combination of what the disease does as well as what some of the drugs do to your body. Filanesib attacks KSP, and KSP is a gene and protein which is not expressed in nerve tissue, so we have seen absolutely no neuropathy with this drug. It is given as an IV and it's given two days in a row every other week.

Slide 68 – Response Data
In this study what was found is that in patients with very aggressive, very relapsed and refractory disease, the response rate overall was about 20%.

Slide 69 – AAG and Outcomes
Also, if you had low levels of a protein in the serum called AAG, your response rate was 33%. This is a way that we may be able to select which patients will benefit most from which therapies, so do look for this drug, which hopefully will be ready soon for trials at a center near you.

Slide 70 – Outline - Aspects of Supportive Care in Myeloma
Before I wrap up, the last category I wanted to cover, were some aspects of supportive care in myeloma, because this is a critically important area. You don't just need chemotherapy for your disease, you also need various aspects of supportive care.

Slide 71 – 2013 ASH Abstract 1694
One of the areas in which myeloma patients can run into problems are so-called thromboembolic events, which means blood clots in the legs, and sometimes those can break off and go to the lungs. Especially when you combine an immunomodulatory drug with a steroid or another chemotherapy, you can be at risk for blood clot formation.

Slide 72 – Study Findings
The study I've highlighted here, abstract 1694, looked at whether hematologists in Ireland used the published guidelines for preventing blood clots. It turned out that only about half of people did follow the published guidelines.

DR. ROBERT ORLOWSKI:
It may be that the ones that did not follow those guidelines still appropriately used prophylaxis. However, this is an area where you as a patient can be an advocate for your own healthcare and ask whether you are on the right treatment to prevent blood clots, or whether you're on a chemotherapy combination that perhaps doesn't require that kind of prophylaxis.

Slide 73 – 2013 ASH Abstract 1686
Another supportive care abstract that I found was interesting was this study, which was done in France, and looked at malnutrition.

Slide 74 – Study Findings
We know that, unfortunately, many patients with myeloma don't have optimal nutritional status. Part of this is because many of the chemotherapy drugs that we give don't improve appetite. Part of it is because the disease changes your metabolism, and sometimes you can have an excellent diet and not gain weight because the cancer uses up all the nutrients. But the question that this survey really asked is who was best at determining whether malnutrition was present or not.

This study looked at 30 French hospitals and blood cancer patients in general were looked at, with 15% of them having myeloma.

According to the standard definition, they found that almost 50% of patients met the criteria for malnutrition. Physicians only identified malnutrition in 35% of patients, patients only identified it in 18%, and relatives only identified it in 14%.

What that means is that, first of all, close relatives may be the worst at determining whether you're malnourished or not, patients themselves are not very good at it, and even doctors are not very good.

I think the take-home message here is that we all probably need to more frequently refer patients to nutritional specialists because we need to be able to maximize your nutritional status and not just throw chemotherapy at you. Nutrition will be important in helping you tolerate treatment and probably get a better outcome.

Slide 75 – 2013 ASH Abstract 1693
Another supportive care study which was interesting looked at whether music therapy was helpful for patients who were undergoing stem cell transplant.

Slide 76 – Study Findings
There was a certified musical therapist involved in this, and they took 82 patients who were undergoing autologous transplant, about half of them had myeloma, and they looked at one group getting music therapy and another not. Then they looked at various symptoms that were present.

Oddly enough, the people who got music therapy at day 7 had more nausea. Now this was done at the Cleveland Clinic, and since the Rock and Roll Hall of Fame is nearby, maybe they played AC/DC or something similar, and maybe that's why people got nauseated. But on a serious note, the important difference was that the patients who did get music therapy actually had a lesser requirement for narcotic use. It's a small study, we need more data, but certainly an interesting finding, and maybe music therapy and other supportive care like this can be of benefit.

DR. ROBERT ORLOWSKI:

Slide 77 – 2013 ASH Abstract 2968
The last study that I thought I would go into is this one, looking at the frequency of skeletal-related events.

Slide 78 – Study Findings
In the past, a large proportion of patients with myeloma got fractures or other problems and there was an impression I think recently with drugs like the bisphosphonates, i.e. zoledronic acid, and with our better chemotherapy drugs, that perhaps that number was much lower. But in this study it showed that even with modern therapy, one-third of patients still had episodes of skeletal-related events. This really points out the need to get drugs like the bisphosphonates and for more research in this area.

Slide 79 – Summary
So that's been a little bit of a whirlwind. But before we go to the questions, I thought I would just generally summarize some of the take-home messages.

Slide 80 – Smoldering Myeloma
In the smoldering myeloma area, we can now define patients who are at ultra high risk for progression, and in the very near future those are people who will be treated like symptomatic myeloma patients. Those are predominantly people that have bony disease by PET or by MRI.

Low risk smoldering myeloma patients will probably be treated more like MGUS with an observation approach and visits may be as infrequently as once per year.

The remaining patients in the high risk and intermediate risk categories should look for well-designed clinical trials like the ECOG E3A06 study, which is looking at lenalidomide versus placebo, because we still feel that observation is the standard of care, but we'd clearly like to improve upon that.

Slide 81 – Transplant-ineligible Myeloma
For patients who are not eligible for stem cell transplant, newer drugs are being introduced, like carfilzomib and ixazomib.

I think there is a greater acceptance that continuing therapy after induction, along the lines of maintenance, is of benefit, although high risk patients still don't do as well and probably should be treated differently.

By the way, there is a national study looking for high risk patients, which gives them lenalidomide, bortezomib and dexamethasone, either with or without elotuzumab, which is another monoclonal antibody that's showing exciting results in myeloma, the rationale being that maybe addition of immunotherapy will help to overcome this high risk disease.

Slide 82 – Transplant Eligible Myeloma
For transplant-eligible patients with myeloma, novel drugs are being used up front like carfilzomib and ixazomib and some of the antibodies are being used as well.

DR. ROBERT ORLOWSKI:
Consolidation and maintenance therapy is important, and especially for high risk patients, it's important to achieve complete remission and to have immunofixation-negative and hopefully minimal residual disease-negative disease.

Slide 83 – Relapsed and/or Refractory Myeloma
In the relapsed setting we've got a lot of new drugs including antibodies like daratumumab, elotuzumab and the SAR drug, novel agents like filanesib and the AKT inhibitor.

Also, we're beginning to understand the biology of myeloma better, which hopefully will allow us to pick the best treatment for you as an individual, not just the generic treatment of choice.

Slide 84 – Importance of Clinical Trial Participation
Finally, when we're looking at the importance of clinical trials – and I think I've tried to highlight this a couple of times during this presentation – the exciting thing about trials is that first of all, the most exciting drugs, like the antibodies, like filanesib, are not yet FDA approved and therefore you really need to be on a clinical trial to get access to them.

Also they have built-in studies of biology of the myeloma, which will allow us to learn more about your, as well as everyone's, myeloma.

One of the things that patients rightfully complain about is the long time that it takes to get new drugs approved, and if we could get more patients on clinical trials we could speed that up, because until the trials are done, the drugs won't be approved. This will bring us closer to a cure for the disease.

Slide 85 – MDACC Myeloma Center
Before we go to the question session, I did want to just put out a both shameless and shameful plug for the Anderson Myeloma Center. We have a toll-free line if you'd like to get information about coming down. This is a list of our doctors. I've provided my email address if you'd like to contact me directly. And there's also an email to ask about myeloma trials. For those of you who are on Twitter, I have a Twitter account where I tweet on new developments in myeloma all around the world, and the handle, as it's called, is @Myeloma_Doc.

Thanks very much for your attention. I hope that this was of help to you. I'll be happy to take questions, and answers hopefully will be appropriate to the questions. Thanks again.

Slide 86 – Question and Answer Session

LAUREN BERGER:
Thank you. We'll take the first question from the web audience, Jack asked, "Can you please explain the P number seen on many study slides? Does a P mean statistically more meaningful?"

DR. ROBERT ORLOWSKI:
Thanks very much for that question, Jack. You're right, the P value is a measure of significance. Generally any number less than 0.05 is felt to be significant. But it's important that you know you can have statistical significance without necessarily clinical significance.

DR. ROBERT ORLOWSKI:
What I mean by that is there was a study in the past presented of a combination of bortezomib with vorinostat compared to bortezomib alone in the relapsed setting. The differences between the two arms of the randomized trial were statistically significant, but when you drilled down to the details it turned out that this translated into a difference of less than a month. Therefore, it's important that the data not just be statistically significant, but that we also get a nice clinically meaningful benefit for the patients. Keep both of those in mind.

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

OPERATOR:
The next question comes from Harry in Michigan. Your line is now open.

HARRY:
Yes, Doctor, was there any information presented, additional information, on secondary cancers associated with Revlimid® for people who have had a stem cell transplant in the past? And not necessarily were on taking Revlimid for maintenance, but prior to maintenance, being a standard of care, of just waited until the disease came back and then went on Revlimid. And what is your opinion of that?

DR. ROBERT ORLOWSKI:
Thanks very much for your question, Harry, and you stay warm up there. It must be pretty chilly.

The data that I think were most interesting in terms of this question of second primary malignancies were from the FIRST trial, which I mentioned at the beginning. What they showed is that, compared to melphalan, prednisone and thalidomide, it looked like lenalidomide and dexamethasone as an initial therapy had a much lower rate of second primary malignancies. Now that's not the same population as people after transplant, but there were not a lot of new data about this whole second malignancy question in the maintenance setting.

There are now studies that are planned, which will look at different durations of maintenance therapy, but I think most investigators in the field still feel that using lenalidomide maintenance after transplant until progression is an appropriate standard of care.

Where we would like to go in the future is to use some of these measures of molecular remission, because it may be that if you achieve a molecular complete remission, the need for maintenance therapy may be decreased or it may be gone altogether. But we're not quite there yet, so I still do lean in favor of LEN maintenance for most of my patients.

LAUREN BERGER:
Thank you for your question, Harry.

We'll take the next question from the web audience and this one's from Richard, "Will monoclonal antibodies be effective for smoldering myeloma? Waiting to get sick is a lot of pressure."

DR. ROBERT ORLOWSKI:
Well, thanks, Richard. That's certainly an understandable sentiment and a great question.

There are studies ongoing in smoldering myeloma with these monoclonal antibodies. I think you're excited and rightfully so because these antibodies in some cases work well by themselves, without any other drugs being added. They're also well tolerated, and the hope is that even if the myeloma does eventually progress, because the antibodies work through a different mechanism, there wouldn't be cross-resistance to other drugs like proteasome inhibitors and immunomodulatory drugs. But for right now those are still all in clinical trials and you should definitely look for them.

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

OPERATOR:
Our next question comes from Steve in Tennessee. Your line is now open.

STEVE:
Thank you very much. Good afternoon, Doctor. I was diagnosed with multiple myeloma down in 2005 and I've been smoldering til 2013. I finally obtained a stem cell transplant, but prior to that I went through seven rounds of chemotherapy. In my fifth and sixth round they added Revlimid along with Velcade® and dexamethasone. My M-spike really did not decrease too much, so in round 7 they decided to go with DCEP. My M-spike dropped from 1.4 to 7.7. At that point I went for my stem cell transplant. I'm currently plus 71 days out. Here's my question. They're talking about maintenance therapy now. Now I did not have a successful outcome when Revlimid 25 milligrams was added in my cycles 5 and 6. Yet now they're thinking about putting me back on 10 milligrams of Revlimid for maintenance. Can I expect any better of a return from the Revlimid for my maintenance?

DR. ROBERT ORLOWSKI:
Well, thanks for that question, Steve. I hope when you said that you went from 1.4 to 7.7 that you meant .77.

STEVE:
I was 1.7. I dropped down to 1.4.

And then the DCEP dropped me from 1.4 to 7.7. No, I'm sorry, .77. Sorry.

DR. ROBERT ORLOWSKI:
Okay, that's what I thought. I was worried when you said it went down from 1.4 to 7.7.

STEVE:
Yeah, I got my points mixed up.

DR. ROBERT ORLOWSKI:
Okay, that can happen, certainly. So it's a good question. One option to consider, which we mentioned a little bit earlier, is to do some kind of consolidation therapy, where rather than just maintenance by itself, you would do maybe two cycles of a combination, especially one that maybe worked well before the stem cell transplant was done.

But you're asking a very important question, which is if drug X, in your case it's lenalidomide, but it could be anything, if drug X did not work well before transplant, is there any point to giving it to me after the transplant. The only thing I can tell you is that there are theoretical data that suggest that the answer is yes. The idea is that, and it's been documented in laboratory studies, is that patients don't just have one type of myeloma, they have many different clones which can be sensitive to different drugs. It's possible that because you just had the stem cell transplant, the high dose melphalan may have killed off the myeloma clones that were resistant to lenalidomide and what you may have left are clones that are sensitive to lenalidomide.

We don't have a lot of data in patients to know whether that's the case or not. What I usually would suggest in a patient like you is to think about not using lenalidomide by itself, but going in with a combination like lenalidomide and bortezomib.

So thanks again for your question.

LAUREN BERGER:
Thanks, Steve.

We'll take the next question from the web audience and this one's from Lara, "For patients who are eligible for an autologous stem cell transplant, is this still the standard of care?"

DR. ROBERT ORLOWSKI:
That's a great question and I tried to cover some of the new data that looked at that. I don't think we have a definitive answer. There is actually an ongoing study, which is being led by the Dana-Farber group and involving the Cooperative Groups and also the French Myeloma Group is involved, where about 1,000 patients are being treated with bortezomib, lenalidomide and dex, and they get randomized either to early transplant or to transplant at the time of first relapse. That's not the same question you're asking. You're asking do I need a transplant or not and this one is asking what the right timing is, but if we find that time to progression on the non-transplant up-front arm is many, many years, that may suggest that it's safe to delay transplant until the time of progression at least.

I feel that transplant is still part of the standard of care. We could argue about whether you should get it up front or whether you should wait until the time that the myeloma first relapses. What I tell patients is that if you get into a complete remission with chemotherapy only and you have the option to collect and store the stem cells, and then wait until relapse to do the transplant, that's appropriate. If you don't get a complete remission, you should definitely do the transplant and hopefully get into complete remission.

But even for those people who get into complete remission, I still have a feeling that the myeloma is most sensitive to therapy at the time that they're first diagnosed, so I still lean in favor of doing the transplant earlier rather than later.

LAUREN BERGER:
Thank you for your question, Lara.

We'll take the next question from the web audience and this one's from Sally. "Can you address the use of curcumin, resveratrol and quercetin supplements in patients with smoldering multiple myeloma?"

DR. ROBERT ORLOWSKI:
Well, thanks, Sally. That's a question that a lot of patients have. You may know that we actually a few years ago did a clinical trial with curcumin here at MD Anderson in myeloma and we did find that some patients had stable disease for long periods of time. But, unfortunately, nobody had a response, meaning a reduction in their myeloma, and because it wasn't a randomized trial, and sometimes myeloma can be stable for long periods without treatment, we couldn't conclude that curcumin was of benefit.

The other drugs that you mentioned, resveratrol and quercetin, these are all natural products that have been shown in laboratory studies to potentially have a benefit. I think that we don't have enough data for us to recommend these routinely for people because there's always a small concern that they may actually interfere with the benefit of chemotherapy. For example, we know that high levels of Vitamin C or high levels of EGCG, which is found in green tea, can directly bind to bortezomib and reduce its efficacy.

I would, though, say that in most instances the three supplements that you've mentioned are probably safe, but I would still make sure that you talk to your doctor or nurse and make sure that you let him or her know that you're on these, so that they can make good recommendations for you about how to integrate them into your treatment, especially if you're on chemotherapy at the same time.

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

OPERATOR:
Our next question comes from Jonathan in Indiana. Your line is now open.

JONATHAN:
Yes, Dr. Orlowski, I'm going to try and get two questions in here quickly. What is your best guess about when the oral proteasome inhibitor will be approved? Just a best guess. And then the real question is in the University of Pennsylvania they're doing a study in leukemia with engineered T-cells. What do you know about it and will that have any good looking possibilities for those of us with multiple myeloma?

DR. ROBERT ORLOWSKI:
Thanks, Jonathan. Especially the second question is a very popular one now with my patients.

In terms of your first one on the question of the oral proteasome inhibitors, the clinical trial that will hopefully lead to the approval of the first oral proteasome inhibitor, which is ixazomib, is still currently ongoing. There's really no way to predict how long it will take because it depends on how much of a benefit there will be. My guess is we're still probably talking about three to five years down the road, so right now trials are your best way to go to get access to that.

DR. ROBERT ORLOWSKI:
In terms of your second question, you're referring to, for those of the folks in the audience that may not know, these are the so-called chimeric antigen receptor T-cells, where basically T-cells from patients are taken out, they're engineered so that they can recognize a target inside cancer cells, and then they're reinfused. There's been really exciting data from Carl June and his colleagues at Penn, looking at this technology in chronic lymphocytic leukemia and in acute lymphoblastic leukemia.

Although that particular type of engineered T-cell would not probably benefit myeloma, the same technology can be changed so that it targets a protein that would benefit myeloma. There are a number of groups that are trying to get that technology into a clinical trial and Penn is one of them, MD Anderson is another. So I think that you should definitely keep an eye on some of the clinical trial portals that are available. For example, clinicaltrials.gov is a great website to look at. Also The Leukemia & Lymphoma Society has a very good trial navigator, and you can also look at the websites of the Multiple Myeloma Research Foundation and the International Myeloma Foundation.

LAUREN BERGER:
Thank you for your question, Jonathan.

We'll take the next question from the web audience and this one's from Steven. "With all the buzz in 2013 about developing standard measurements for minimal residual disease, has there been any progress in that regard, and if so, when might we expect to see its regular application in the clinical setting?"

DR. ROBERT ORLOWSKI:
Thanks, Steven, that's a very hot area in myeloma. There are now committees that are working to try to standardize some of these measurements – one of them is being organized by the International Myeloma Foundation and also the International Myeloma Working Group. Probably the first one that will be widely available – and in fact already is in many places, including MD Anderson – is so-called flow immunophenotyping. This is a way where you can take the bone marrow and look at the plasma cells to decide whether they are normal or abnormal and get an idea of how much disease is left, if any. That approach probably may be available to you now.

What we're looking to do is develop easier tests, for example, that would only rely on the peripheral blood, so that patients don't need to get so many bone marrow aspirates.

Then we still have to show that using that information helps us to manage patients better. Clearly people that have flow-negative or other of these measurements negative, MRD-negative disease, are going to do better than those who are MRD-positive. The question is whether if we take those that are MRD-positive and treat them, can we convert them to MRD-negative and improve their outcome, so that we can be sure that we're not just throwing more drugs at them because we can.

LAUREN BERGER:
Thank you for that question, Steven. We'll take the next question from the telephone audience, please.

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

PAUL:
Hello, this is Paul. I was calling to ask the doctor, I've been in treatment since '02. I've had almost every drug there is. Luckily I'm still alive. The question I wanted the doctor to address is last combination I had was EPOCH and I got almost seven years out of that. Now my numbers are up again, where I'm ready for treatment again. And what – being I had all these different agents, what would be a sensible drug to choose?

DR. ROBERT ORLOWSKI:
Well, thanks very much, Paul, for that question. EPOCH is a little bit of an unusual combination to do against myeloma. It's more typically used for patients with lymphoma although it has drugs that do work against myeloma. What your next option should be I think really depends on what other treatments you've had before, and because you have such a very specific question, what I would recommend you do is I've got my email address on one of the last slides in the presentation, if you could email me with your information and tell me what drugs and combinations you've gotten, I'd be able to email you back and let you know what I thought. Of course, I have to tell you the disclaimer, which is that it's always better for patients to come for a consult in person because it's not just your history, but how you look and what you want that are important. But nonetheless, I might be able to give you some guidance by email that way.

LAUREN BERGER:
Thanks, Paul, for the question, and thank you, Dr. Orlowski, for offering that.

We'll take the next question from the web audience and this one's from Joel. "What are the pluses and minuses of Velcade delivery, via subcutaneous injection versus IV administration?"

DR. ROBERT ORLOWSKI:
Great question, thanks for that, Joel. Bortezomib is used both alone and in combination for a lot of different scenarios, and as you're asking, it can be given either intravenously or subcutaneously. There's only one study that compared them head-to-head, which was again a French study, and it showed that the two approaches were virtually identical in terms of outcome. The big benefit with the subcutaneous was that there was much less neuropathy and a little bit less thrombocytopenia or low platelets as well.

We don't have randomized data in other combinations, but our experience and I think this is true at many places, is that the subcutaneous route is much better tolerated, and I would definitely go with that if you have that option.

Only a few people really can't do subcutaneous because occasionally you will have people that have very severe skin reactions due to the injection, and then they prefer to get it IV. Otherwise I think it's probably best to give it subcutaneously in virtually every patient.

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

OPERATOR:
Our next question comes from Patricia in New York. Your line is now open.

PATRICIA:
Thank you. Thank you, Doctor, for a wonderful meeting. My question is very similar to the gentleman that called in earlier with the Revlimid. I was diagnosed with Stage III in 2008. Did a stem cell in 2009. Went on Revlimid for several months, maintenance. Had to go off because of low platelets and immune system problems. I stayed myeloma drug-free until January of 2014, when my PET scan showed I guess early relapse. My protein is good, my blood work is good. I haven't had bone marrow done, but they've decided to treat me with Revlimid maintenance 5 milligrams. I feel the same way. I had such a problem in the beginning, what would be the good of putting me on it now? Although I did listen to what you said about the cloning and that it could work with this. My question is would you advise I stay with the Revlimid? What about connecting it with bortezomib? Or you mentioned the three combos in your – later part of the relapse process, which was carfilzomib, pomalidomide and the dex. Could you give me some kind of a response to this?

DR. ROBERT ORLOWSKI:
Sure. Thanks very much for your question, Patricia. A lot depends here on how much disease was detected on the PET scan. PET scan is a very good way to detect early disease and if, for example, you are in the – I would say lucky category, to have only one area of involvement on the PET scan – one option to consider is maybe to just do radiation to that one area and not do chemotherapy. Occasionally people will relapse with localized disease.

In the event that you have multiple areas that were positive on the PET scan, though, I think probably some kind of treatment would be appropriate. Again, it's tough to second-guess your doctors without knowing your full history, because it sounds like they're making a good recommendation.

The fact that you had problems with low blood counts when you took the lenalidomide right after transplant, doesn't mean that the same thing will be true now, because probably your bone marrow has recovered to a much better level now than it did then, especially if you've been off of treatment for a long time.

So I would say that the benefit potentially of the lenalidomide at this time is that it could prevent you from having a clinical relapse, meaning that the protein levels are going up and you're having fractures and other problems like that. I would probably lean in favor of doing it, although again, more detail about your case in a formal consult would always be of benefit. So good luck.

LAUREN BERGER:
Thank you for your question, Patricia.

We'll take the next question from the web audience and this is from Cary , "Can you please explain a little bit more about what myeloma is and why it is a blood cancer, not a bone cancer, since the cancer is in the bone marrow?"

DR. ROBERT ORLOWSKI:
It's a very good question, Cary. The reason it's considered a blood cancer is that the type of cell that becomes abnormal is a cell which is made by the bone marrow, just like other blood cells, like red blood cells, white blood cells and platelets. It just so happens to be in the bone because that's where the bone marrow is usually found and where your blood cells are made. But for example, if you look in the blood

DR. ROBERT ORLOWSKI:
of patients with myeloma, especially when they're newly diagnosed, or when they have relapsed or refractory disease, using very sensitive tests, you can see some circulating myeloma cells in the blood. Those are the two main reasons that it's considered a blood-related cancer, even though as you're correctly pointing out, it can have a lot of bone problems with it.

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

OPERATOR:
Our next question comes from John in Oregon. Your line is now open.

JOHN:
This question, I've been on Revlimid for four years and the doctor told me that I had a complete remission earlier this year. And I've noticed on my blood tests my LGA has gone up about 100 points in the last six months. Does this mean that the myeloma is relapsing or is this something that could be rendered stable with the Revlimid-dexamethasone regimen that I'm currently on?

DR. ROBERT ORLOWSKI:
John, before you go, is that LDH, lactate dehydrogenase that has gone up?

JOHN:
LDH. It had been in the 300 – LGA, I'm sorry. Am I getting the right?

DR. ROBERT ORLOWSKI:
Or is it IgA?

JOHN:
Maybe it's IgA.

DR. ROBERT ORLOWSKI:
Okay. I'm not completely sure which number we're dealing with, so maybe you can email me. The two that sound the closest, there's something called LDH or lactate dehydrogenase, and this is a protein which sometimes is elevated in myeloma, although it also can be elevated by other processes like infection or inflammation. If the LDH is up, but the myeloma numbers look the same, usually one would look for some other cause and a bone marrow may still be useful, though. If it's the IgA or immunoglobulin A, that may be going up for a couple of reasons. Number one is if you have an IgA type of myeloma, the IgA may be going up because the myeloma is increasing, in which case you probably do need to do something different. Or if you have, for example, an IgG myeloma, and your IgA is going up, usually that would be a good sign and that would indicate that perhaps your immune system is recovering and making more antibodies, which are basically what immunoglobulins are.

So if one of the two I mentioned is not the test you're talking about, just email me and, by the way, congratulations on your complete remission.

LAUREN BERGER:
Thank you for your question, John.

We'll take the next question from the web audience and this one's from Barbara. "I received a Doxil®-Velcade combination as part of my pre-transplant treatment. I don't know how common the use of Doxil is, but I know there is a major shortage of the drug. Is this affecting myeloma treatment?"

DR. ROBERT ORLOWSKI:
Thanks for that question, Barbara. The pegylated lyposomal doxorubicin, that's the long name for the drug that you got, is one of the approved therapies for myeloma. I actually led the clinical trial that led to its approval. It is approved in the relapsed setting and it is used less often in newly diagnosed patients. I think that there may be some people out there who have been affected by the shortage, and as you know, this is not just a problem with this particular drug. There are a lot of generic drugs and also trade drugs of which there are shortages out there and that are affecting people. While there really isn't a good way to get an idea of how many people are affected, in my mind even one patient being affected is too many. I think this is an area where you can perhaps help by touching base with your Congressmen and women and encouraging them to have this high on their radar because we do really need to make sure that drugs are available when they're needed.

LAUREN BERGER:
Absolutely. Thank you for your question, Barbara. And for those of you who have your packet, after the program you can refer to the LLS Advocacy flyer for information on how to get involved, including how to reach your Congress people. So thanks for that good question.

We'll take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Phil in Texas. Your line is now open.

PHIL:
Great. Thanks for your time, sir. Two questions that are kind of related. A person in complete remission post-transplant, I'm wondering if there's any therapy recommended. I'm 0.0 and have been for over a year. I'm just wondering if there's anything recommended. And secondly, more specifically, wanted to find out if there's any benefit of using Zometa® infusion as a way to curb relapse.

DR. ROBERT ORLOWSKI:
Thanks for those questions, Phil. Even patients in complete remission, the study that was done in the United States, looking at lenalidomide versus placebo after transplant as a maintenance, even those who were in complete remission did seem to benefit. Even though you've not been on maintenance before, you could start it now and hopefully still have a nice benefit.

In terms of your question about some of the bisphosphonates like the zoledronic acid, there was one study in particular that suggested that they may have a direct anti-myeloma effect, which was a British trial, where people who got zoledronic acid as opposed to an oral version of a bisphosphonate called clodronate, which is not available here, the ones that got zoledronic acid seemed to live a few months

DR. ROBERT ORLOWSKI:
longer on top of their benefit from their regular chemotherapy. Remember that it's approved for people that either have myeloma-related bone disease like fractures or lytic disease, or people that have osteoporosis, which is felt to be due to myeloma. If you don't have any obvious bone disease, that's not an area where the drug is approved. It does have a small risk of some side effects, which can include jaw osteonecrosis as well as kidney damage, so it's not to be given to everybody lightly.

LAUREN BERGER:
Thank you for your question, Phil.

We'll take the next question from the web audience from Keith and Keith asks, "How long can one safely take Revlimid?"

DR. ROBERT ORLOWSKI:
Thanks, Keith. Really there's no particular upward limit that we know of. We follow patients closely, monitor their counts, make sure they're doing well, and as long as they're not having any side effects or as long as their disease is not progressing, it's okay to continue the lenalidomide. The one exception is if you're thinking about a stem cell transplant in the future, one of the downsides to lenalidomide is that if you're on it for a long time, it can reduce the number of stem cells that can be collected. Therefore if you're thinking that you're going to be on lenalidomide and you haven't had a transplant, but you would like to, or even not rule out the possibility, you should definitely have the stem cells collected first before you're on lenalidomide for too long.

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

OPERATOR:
Our next question comes from Thomas in Tennessee. Your line is now open.

THOMAS:
Hi, Doctor, I'm in remission, but I have things that people don't answer quite often, is the amount of bone loss and bone fractures, I've had quite a few, I've had some kyphoplasty. And then the amount of just total bone weariness, tired all the time. What are some of the therapies that can be done for these particular things and how long does it usually take for the bones to get back to a normal – where you don't have to worry about falling down and breaking a vertebra?

DR. ROBERT ORLOWSKI:
That's a good question, Thomas. I think that the problems you're having are hopefully all due to the myeloma, but it is important to remember that there can be other factors that contribute to bone problems, even if your myeloma is in complete remission. For example, you may want to have your doctor, or perhaps even an endocrinologist, to make sure that you're not Vitamin D deficient, as one example, because if you are, that can reduce the ability of your body to absorb calcium, which of course is necessary for good bone growth. Also, we have a very active bone health program here at MD Anderson and what we find is that sometimes zoledronic acid by itself is not enough to rebuild bone in

DR. ROBERT ORLOWSKI:
patients with myeloma, even if they're in complete remission, and there are other drugs which we can sometimes use that may help in that process. For example, there's what's called a recombinant parathyroid hormone, which can be used as a drug. It's an injection and it can help to improve bone density. So those may be options for you. But I think the fact that you're in complete remission will certainly be a big plus.

LAUREN BERGER:
Thank you for that question.

We'll take the next question from the web audience and this one's from Linda. "Do you regularly use PET or CT scans for regular disease evaluation?"

DR. ROBERT ORLOWSKI:
Thanks for that question, Linda. I think that more and more people are using PET scanning and also MRI scanning to evaluate the disease status of myeloma. You may have heard the caller earlier whose disease was looking like it was coming back on PET scan, even though the numbers were fine. So I do think that PET scan can be very valuable. Of course, I think we also have to be careful in how we use it because it does expose patients to some irradiation, and that by itself can be an issue. It's not inexpensive, and sometimes there can be issues with insurance coverage. But those issues aside, I do think that it's an important test to monitor, although usually the blood and urine tests in the majority of patients are quite good as well.

Slide 87 – Resources

LAUREN BERGER:
Thank you for your question, Linda, and thank you all for your questions, and thanks to Dr. Orlowski for all the time and expertise you shared with us today. We hope this information will assist you and your family in your next steps.

The Leukemia & Lymphoma Society also offers online chats for myeloma patients and chats for caregivers. Each of these chats is held on Tuesday evenings from 8 to 10 PM Eastern Time. The chats are moderated by oncology social workers and they provide forums for patients and caregivers to share experiences and to support each other, and the chats are free. For information on how to participate, there is a flyer in your packet, or you can go on the web to LLS.org/chat, or you can contact an Information Specialist at The Leukemia & Lymphoma Society.

If we were not able to get to your question today, please call The Leukemia & Lymphoma Society Information Specialists at 800-955-4572, or you can reach us by email at infocenter@lls.org. We can provide you with information about myeloma research, searching for clinical trials, and other questions that you may have about treatment and also about financial assistance for treatment.

Also we hope that you will consider joining the Cancer Experience Registry for multiple myeloma. This is a new initiative from the Cancer Support Community to identify and to raise awareness about both the social and the emotional needs that accompany a myeloma diagnosis. And you can join the registry at www.cancerexperienceregistry.org.

LAUREN BERGER:
Please help me thank Dr. Orlowski for sharing his volunteer time with us today.

On behalf of The Leukemia & Lymphoma Society, thank you all for sharing your time. Goodbye and we wish you well.

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