Robert Z. Orlowski, MD, PhD
December 19, 2011

Slide 1: Myeloma–Updates from the American Society of Hematology Annual Meeting

OPERATOR:
Hello, everyone, and welcome to *Myeloma–Updates 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.

Slide 2: Moderator: Lauren Berger, MPH

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

We have almost 1,300 people participating from across the United States and international participants from Australia, Canada, Guatemala, Peru and Saudi Arabia.

We'd like to thank and acknowledge Celgene Corporation, Millennium Pharmaceuticals and Onyx Pharmaceuticals for their grants to support today's program.

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?

JOHN WALTER:
Thank you, Lauren. I'd like to add my welcome to all the patients, caregivers and healthcare professionals on the program today. We are fortunate to have as our presenter today Dr. Robert Orlowski, one of the nation's leading experts in myeloma. We appreciate Dr. Orlowski's dedication to supporting the mission of The Leukemia & Lymphoma Society through his research and care of patients with blood cancers. I would like to thank him for taking the time out of a busy schedule to provide us with the latest information on myeloma from the ASH annual meeting.

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

Since 1954 LLS has awarded more than $814 million to fund research, specifically targeting blood cancers. We will continue to invest in research for cures and programs and services that improve the quality of life for patients and their families. This program is one step on the road of your journey to managing your life with myeloma.

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

Slide 3: Robert Z. Orlowski, MD, PhD

LAUREN BERGER:
Thank you, John. I am now pleased to introduce Dr. Robert Orlowski, Chair of the Southwest Oncology Group Myeloma Committee and Professor, Departments of Lymphoma, Myeloma and Experimental Therapeutics in the Division of Cancer Medicine at the University of Texas MD Anderson Cancer Center in Houston, Texas. Dr. Orlowski, we are so privileged to have you with us today and I will now turn the program over to you.

DR. ROBERT ORLOWSKI:
Lauren, thank you very much for the kind introduction and I also would like to welcome all of the listeners on the line and thank you all for joining. I also would like to thank The Leukemia & Lymphoma Society for all that they do to support myeloma research as well as myeloma patients. And then finally I'd like to thank all of the presenters of some of the abstracts that I'm going to discuss for you, because most of them were very happy to provide me with some of the slides that you're going to see, in order to allow the information that's important to myeloma therapy to be given out to the patients.

Slide 4: Outline
Just to give you an overview of what I'm going to talk about, I'm going to try to cover a couple of different areas. First I'll show you some new information about the biology and course of myeloma, then talk a little bit about what we do for so-called asymptomatic or smoldering disease, also what we do for initial therapy in newly diagnosed symptomatic patients who are either not eligible for transplant or are eligible for transplant, a couple of words then about transplant itself and maintenance, also an update on relapsed and refractory myeloma and then a little bit on developments in supportive care. So as you can see, there's a lot to cover and I'm going to go through the slides to try to show you in all these areas.

Slide 5: 2011 ASH Abstract 994
First of all, focusing on new information about disease biology. We know from studies of patients who are transplant candidates that there are a number of different chromosome abnormalities that can be found in myeloma and those abnormalities sometimes can have an impact on prognosis. Some of them give a better than average prognosis, some an average and some a less than average prognosis. And in the future we may be treating patients differently, based on the results of those tests.

So this abstract, which is from the French myeloma group, looked at whether these abnormalities were present also in patients who were not eligible for transplants.

Slide 6: Chromosomal Changes & OS
And you can see here on the slide, talking about chromosomal changes and overall survival, that three abnormalities in particular had a negative impact on survival and those three were deletion of chromosome 13, translocation of 4;14, and deletion of 17p. These are, by the way, the same abnormalities that have a poor outcome in younger patients. But the good news for older patients is that it turned out that the 4;14 translocation was less frequently seen in this older or more mature patient population than in younger patients.

DR. ROBERT ORLOWSKI:
So certainly the message here is that you should have this information available when you're diagnosed or when your myeloma relapses, to at least get a better idea of prognosis.

Slide 7: 2011 Ash Abstract 332
One of the problems with these prognostic criteria in the past has been that we did not have good ways of overcoming poor prognosis when it was identified. And fortunately, we think that those times may be coming to an end. Part of that is based on this study that I'll be discussing, which was a trial done jointly by the Dutch and German myeloma study groups.

Slide 8: Study Design
What they did is compare two different treatment approaches for newly diagnosed patients. On the left hand side of the slide in green is the older standard therapy, where patients got VAD or vincristine with doxorubicin and dexamethasone, followed by transplant, and then thalidomide for maintenance. And on the right side in the yellow boxes, patients got instead of VAD, they got PAD, which is bortezomib with doxorubicin and dexamethasone, again followed by transplant, and then followed by bortezomib maintenance therapy.

Slide 9: In Both Study Arms
And the curves here show that for progression-free survival on the left, as well as overall survival on the right, the group that got bortezomib during induction, as well as bortezomib for maintenance therapy, had a very good outcome even if they had the worst of those chromosome abnormalities, which is basically that of deletion of 17p.

And for example, if you look at the blue curve, which is deletion of 17p, who got bortezomib therapy, and compare it with the green curve, which is deletion of 17p without bortezomib, you can see that the patients who got bortezomib did much better and although their outcome is still not as good as if you didn't have deletion of 17p, it certainly was much improved.

And I think the take-home message from this study is that if you have high risk disease, especially with that deletion 17p abnormality, using bortezomib early and in a number of different ways, such as during induction and maintenance, is an important aspect to improving outcomes.

Slide 10: 2011 ASH Abstract 996
I'm going to switch now to talk about second primary malignancy because a number of studies presented last year at ASH and also this year, raised concern among patients and doctors and healthcare providers about the possibility that some of the therapies that we're using may cause damage to normal cells and cause what are called SPMs or second primary malignancies.

And the study here that I'm going to show you is from an Italian group. They looked at 2,500 patients almost, with myeloma, who were treated, and tried to identify what was the risk of developing second cancers. And that's shown in these slides, based on different types of therapy.

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Slide 11: Cumulative Incidence of SPMs

If you look at the right lower corner where you see patients who got melphalan, but no immunomodulatory drugs, you can see that there was a small risk of developing second cancers. If patients got melphalan and either lenalidomide, which is the upper right, or melphalan with thalidomide, which is the lower left, it looks like the risk was higher. And also in the upper left patients who got lenalidomide with either dexamethasone or cyclophosphamide, also had something of a risk. However, it's important to remember that patients in these age groups often can develop second cancer, which may have nothing to do with their myeloma or with their therapy.

Slide 12: SPMs & Risk of Progression

And in fact, when the risk of second cancers was compared with the risk of progression in this graph, the risk of progression is the white curve and the risk of second cancers are in the yellow and blue curves. And you can see that comparing the two, the risk of complications and even death from multiple myeloma is still very much higher than the risk of developing a second cancer. So we are still at the stage where myeloma needs to be enemy number one.

Slide 13: Observed vs. Expected SPMs

When the Italians looked at what were the observed numbers of second cancers versus what would have been expected, based on studies of the Italian Cancer Registry, you can compare in the second and third columns, observed cancers versus expected cancers. And you can see that at least in this analysis, the observed numbers of cancers were actually lower than the expected number of cancers, which would suggest that at least in this patient population, the drugs that were used did not increase the risk of second cancers.

Slide 14: Investigator Conclusions

And certainly those were the conclusions of the study investigators. Although I think and all would agree that more study of this important area is warranted.

Slide 15: 2011 ASH Abstract 823

And then a second study of second cancers was presented by the group from the University of Arkansas.

Slide 16: SPM types

They used so-called total therapy in various forms. And they looked at what proportion of patients did develop second cancers after total therapy, comparing with and without thalidomide as well as with and without bortezomib.

Slide 17: Cumalative Incidence

And you can see in these curves that it doesn't look like the addition of thalidomide increased second cancer rates and also it does not look like the addition of bortezomib increased second cancer rates. Although you can see that up to perhaps 10 percent of patients, going out to about ten years of follow-up, were at risk of developing second cancers.

DR. ROBERT ORLOWSKI:

And certainly this is something that will need close attention because we want to make sure that, if possible, we detect those early and start treatment for those early as well.

Slide 18: Outline

I'm going to switch now to asymptomatic or what used to be called smoldering myeloma. And these are patients who in the past we did not automatically treat because a fair proportion of them would never develop symptomatic myeloma and the thought was that we should therefore spare them the complications of chemotherapy, at least until their disease became symptomatic.

Slide 19: 2011 ASH Abstract 991

That approach may be changing because we now do have ways to identify patients in the smoldering category who are at high risk.

Slide 20: Study Design

And you can see here the types of criteria that were used. These were patients who had at least 10 percent involvement of the bone marrow and a monoclonal protein of at least 3 grams or the plasma cells that were present had to be abnormal myeloma cells. And these patients were randomized either to observation, which would be the current standard, or to nine cycles of lenalidomide with dexamethasone, followed later by maintenance with lenalidomide. The main end-point was time to progression to active multiple myeloma.

Slide 21: TTP to Active Disease

And you can see here that the patients in the yellow curve, who got lenalidomide and dexamethasone, were much less likely to progress to active myeloma than the patients who got just observation alone, which are in the blue curve. In fact, half of the patients in the observation arm had progressed to myeloma within two years, whereas not even half had yet gotten to that point, with about three years of total follow-up with lenalidomide and dexamethasone.

Slide 22: Second Primary Malignancies

Interestingly, there were three patients who got lenalidomide, who were identified as having second cancers, but in all of those patients those appeared to be problems that they had before they ever went on therapy with lenalidomide. For example, two patients had prostate cancer that was diagnosed, but both of them had some evidence of prostate overgrowth even before they went on the study. And we know that those are patients at increased risk of prostate cancer. And the one patient who had polycythemia vera, which is the disease of red blood cells, turned out to have a mutation that helped to facilitate that disease developing. And this mutation was present again before he ever got on treatment with lenalidomide. And so that shows that some of these second primary cancers that are arising are probably cancers that the patients were already either predisposed to or may already have had, but at just too low a level to actually detect.

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Slide 23: Overall Survival from Inclusion
And here you see the overall survival curve. And the study is still relatively immature, but it does look like the lenalidomide and dexamethasone group in yellow is living longer than the patients who got no treatment. And certainly that's something that could change the standard of care for patients who have their smoldering myeloma.

Slide 24: Outline
For those patients who already have myeloma that is symptomatic and need to be treated, there are a couple of new options to consider for initial therapy.

Slide 25: 2011 ASH Abstract 475
One of them is a combination of melphalan with prednisone and lenalidomide.

Slide 26: Study Design
And that's based on a large three arm study that was done, comparing melphalan and prednisone, or MP, to MP with lenalidomide or MPR, or MPR followed by lenalidomide maintenance, which is the top group there.

Slide 27: Progression-free and Overall Survival
If you look at the study that showed the outcome in terms of progression-free survival, the group that got MPR followed by lenalidomide maintenance, had a much lower risk of disease progression. And it seemed like there was not yet a difference in survival, but longer follow-up may show us that.

Slide 28: Second Primary Malignancies
Again looking at the question of second primary cancers, you can see that the risk of progression of myeloma to complications or death, which is the green curve, is much, much higher than the relatively low risk of second cancers. Which again points out that what is still important is to make sure that we get the myeloma taken care of, because patients suffer much more from that. And the risk of death from a second cancer or even of developing a second cancer is much, much lower, fortunately, than the risk of complications or death from myeloma.

Slide 29: 2011 ASH Abstract 478
In addition to lenalidomide, patients who are not transplant candidates may use bortezomib-based regiments.

Slide 30: Study Design
And this study compared three different bortezomib-based regimens, including bortezomib with dexamethasone, bortezomib with thalidomide and dexamethasone, or bortezomib with melphalan and prednisone.

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Slide 31: Best Response Rates
If you look at the overall response rates, you can see some differences between them, but not really large enough to be what we would consider statistically significant.

Slide 32: Overall Survival
If you look at the overall survival, you can see that the curves are almost identical, which tells you that the outcome of these patients is very good, no matter which of those three combinations they take.

Slide 33: Patient-reported Quality of Life
And then finally if you look at the patient-reported outcomes, you can see that the patients in the blue curve and the green curve, which were bortezomib with dex or bortezomib with melphalan and prednisone, have the best maintenance of their quality of life. And what that says is that those two, as opposed to bortezomib with thalidomide and dexamethasone, would probably be the best way to go because they combine an excellent outcome with a lower risk of side effects and maintain quality of life much better. And certainly we want patients not just to live longer with myeloma, but also to have the best possible quality of life.

Slide 34: 2011 ASH Abstract 476
And then finally in terms of bortezomib, melphalan and prednisone,

Slide 35: MMY–3002 Study Design
we did get five year follow-up from the study and this was a trial that compared melphalan and prednisone versus melphalan, prednisone and bortezomib in almost 700 patients.

Slide 36: Overall Survival
With five years of follow-up, you can see that the patients who got VMP, which is the yellowish curve, had a better outcome in terms of survival than the patients who got melphalan and prednisone. There actually was a more than 30 percent reduction in the risk of dying if you got VMP. And on average the VMP group lived 13 months longer than the group that got MP.

Slide 37: Impact of High-risk Cytogenetics
If you look at high risk cytogenetics, you can see that high risk cytogenetics was still an influence on outcome and still did reduce the benefit. So we do still need to do more for these high risk features.

Slide 38: OS in Those Receiving Subsequent Therapies
We also know that from these studies if you got the VMP regimen, and then had to get a second treatment after that, one of the concerns we've had over the years is that if you get a more aggressive initial treatment, that the relapse may be more resistant to therapy and therefore the outcomes may be worse. And in fact, what these curves show you is that that's not the case because the VMP curve in yellow, those patients still did better in their second therapy, than did patients with melphalan and prednisone. Which means that drug resistance is not really an issue yet at this time.

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Slide 39: VMP Compared to MP then V

And the other thing that we've debated for a long time is is it better to give your best drugs up front, or should you give one or two and save one or two for later because the disease will relapse. And I don't think we know the answer yet for sure to that question, but here is a study that shows you what happens to patients that got VMP up front, compared to those who got MP first, and then bortezomib at the time of relapse. And you can see that getting VMP early, those patients did better, and I think that's a strong argument to support that getting the best therapy up front gives you the best long term outcome.

Slide 40: SPMs: Exposure-adjusted Incidence

And then finally there was an interpretation of the data to look for second primary cancers and the conclusion was that overall there was no increased risk of second cancers by adding bortezomib to melphalan and prednisone. Both of the groups actually had at least the rate expected or in some cases an even lower rate than expected.

Slide 41: 2011 ASH Abstract 477

And then finally this abstract from the Spanish Myeloma Group looked at the use of maintenance therapy with either bortezomib and thalidomide or with bortezomib and prednisone.

Slide 42: Study Design

And this was after initial therapy with bortezomib, melphalan and prednisone or bortezomib with thalidomide and prednisone.

Slide 43: OS According to Maintenance

You can see here that overall survival was very good for this group.

Slide 44: Cytogenetics & Maintenance

These are patients who in the past used to live only on average maybe two to three years and now you can see that overall survival is reaching four to five years or more, so there has been an improvement. And although we don't know which of the maintenances are better, we do know that they improve outcomes in both standard risk as well as high risk.

And I think this really shows that more and more for both transplant-eligible and transplant-ineligible patients, we are going to an approach where even after transplant or after induction, maintenance therapy is added because as long as it's well tolerated, it seems to improve the response quality and also to improve overall survival.

Slide 45: Outline

Let's now move over to initial therapy for patients who are transplant candidates. And standard options at this point would be things like lenalidomide and dexamethasone or bortezomib with dexamethasone or three drug combinations like bortezomib with lenalidomide and dexamethasone.

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Slide 46: 2011 ASH Abstract 631
One new one that we may be using in the future is carfilzomib with lenalidomide and dexamethasone. And probably many of you know that carfilzomib is a new proteasome inhibitor that has potentially some benefit compared to bortezomib because it seems to cause less peripheral neuropathy.

Slide 47: Schedule & Dosing
The way the drugs were dosed is that the lenalidomide was given daily for 21 out of 28 days. The dexamethasone was given only one day per week. And the carfilzomib was given on day 1 and 2, 8 and 9, and 15 and 16.

Slide 48: Toxicities: All Grades
Here you can see some of the side effects and as I mentioned earlier, the rate of neuropathy is relatively low. You can see about 20 percent of patients had any neuropathy and all of it was grade 1 and 2, which would be mild to moderate, and there were no severe episodes of neuropathy.

Slide 49: Best Responses
If you look at the best responses that are shown here, some of the responses, even in the unfavorable cytogenetic groups, are as high as 100 percent.

Slide 50: Responses by Dose Level
And if you look here at the responses by dose level, even some of the lower dose levels, like 20 milligram per meter squared or 27 milligram per meter squared, had virtually 100 percent response rates.

Slide 51: Response & Treatment Duration
And then finally you can see in this graph and table that even just four cycles was often enough to give a 100 percent response rate and after just four cycles, 71 percent of patients were in a complete remission. And this is much higher than we used to be able to achieve with chemotherapy plus a transplant. Let alone only four cycles of chemotherapy with no transplant. So this may be an approach that we'll be using in the future.

Slide 52: 2011 ASH Abstract 479
Other approaches that I thought were also exciting, there is a new proteasome inhibitor being tested in trials called MLN9708, which is an oral proteasome inhibitor.

Slide 53: Study Design
And these investigators looked at it for newly diagnosed patients with lenalidomide and dexamethasone. The 9708 or oral proteasome inhibitor was given once per week in the first three weeks out of a four week cycle. So the exciting thing about this is in part that these are all oral drugs now, with the proteasome inhibitor, with dexamethasone and with lenalidomide. You don't have to come to the hospital or the clinic or the office for IV therapy at all, which is I think kind of exciting.

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Slide 54: All Adverse Events
If you look at some of the adverse events, the main differences appear to be, compared to bortezomib, that there is less neuropathy, which is good, but there are probably more GI side effects like nausea and vomiting, and also there are some rashes that occur, which are probably more frequent than with bortezomib, although the only way to know for sure is a randomized trial.

Slide 55: Preliminary Responses
Very excitingly, out of the first 15 patients who could be evaluated, 100 percent of them had at least a partial response after just four cycles. And most of them were in the first cycle of therapy. And so an all oral regimen that looks like gives you high response rate, high response quality and very rapid responses. Certainly something that we should follow up on in the future.

Slide 56: Outline
Let me spend a few minutes talking about transplant and also about maintenance therapy.

Slide 57: 2011 ASH Abstract 333
From MD Anderson here, we actually looked at our database to look at whether standard abnormalities in chromosomes can make a difference. I talked about some of the high risk features before, like 17p and 4;14 and 4;14 translocation, but there also are what we consider good risk or standard risk abnormalities. And what this study did was to look at whether they had an influence on the outcome with transplant. And they were compared to patients with completely normal chromosome findings.

Slide 58: Non-high Risk Abnormalities & Outcomes
You can see in this table that if you compare the normal patient versus those who had cytogenetic abnormalities that were not considered high risk, in particular if you look at the complete response or CR values, the patients who had the non-high risk abnormalities still had a lower likelihood of getting into a complete remission.

Slide 59: Overall Survival
And if you look at the overall survival, the patients with a normal cytogenetic profile in red, still did better than the patients that have the so-called non-high risk abnormalities in blue.

And this needs to be studied further, but it does suggest that even the quote-unquote good risk abnormalities are not so good to have. And it also suggests that if patients have abnormalities at the time of transplant, perhaps additional therapy to try to get rid of those myeloma cells would be of benefit.

Slide 60: 2011 ASH Abstract 504
Another option about transplant is not just to do it once, but to do it more than once if the disease relapses. And this particular study I'm going to highlight looked at what is the benefit of a second autologous transplant if patients have relapsed after a first autologous transplant.

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Slide 61: Long-term Outcomes
You can see here, comparing the autologous transplant 1, versus the autologous transplant 2, patients who got a second transplant had a lower likelihood of responding at one year and the complete response rate was lower and the relapse at three years was lower as well. While the time to relapse was 12 months for the second transplant versus 18 months for the first. That argues that after a second transplant some kind of maintenance therapy should be used.

Slide 62: OS and Time to First Relapse
And it looked like the patients who did best after a second transplant were those who had at least a three year remission after the first one.

And in particular we know that patients after just a remission of less than 12 months will usually not do well with a second standard transplant.

Slide 63: 2011 ASH Abstract 636
One interesting study that looked at using vaccinations against the myeloma protein after transplant was presented.

Slide 64: Study 2: Overall Survival
And although I don't have a lot of time to go into the detail about that, it's interesting that if you look at these curves, the patients who got the vaccine in red did better than the patients who did not, in blue. And we actually at MD Anderson do have a study we're about to start, looking at this type of vaccine along with a T cell approach, to try to get rid of minimal disease after stem cell transplantation.

Slide 65: 2011 ASH Abstract 827
The other thing I wanted to highlight in the maintenance or consolidation area, was this study from the Italians,

Slide 66: Study Design
where they gave patients after transplant, bortezomib with thalidomide and dexamethasone.

Slide 67: Survival by Molecular Tumor Burden
The goal was to try again to get even lower levels of disease and you can see in this graph here that patients in the green curve, who had very low levels of myeloma, based on a so-called PCR or polymerase chain reaction study, had a lower likelihood to progress, and a much greater likelihood to be alive, than patients who still had a lot of residual disease. And many of these were patients who were in complete remission by the standard criteria. And I think what that says is that we need to try even after a transplant to drive the disease down as low as possible, as long as patients are tolerating therapy well. Because lower disease levels of myeloma are better, of course, than higher disease levels.

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Slide 68: Outline

Let me now switch gears and talk about relapsed or refractory myeloma because unfortunately, despite all of the therapies and new innovations that I've described, the majority of patients will still have a relapse at some point.

Slide 69: 2011 ASH Abstract 811

Two studies that were presented, which were important, were the so-called VANTAGE Studies, which looked at combining bortezomib and dexamethasone with a third drug called vorinostat, which is a drug in a class of drugs called histone deacetylase inhibitors.

Slide 70: Trial Design

So this was a randomized trial where half of patients got bortezomib and dex with a placebo, and the other half got bortezomib and dex with vorinostat.

Slide 71: Response by EBMT Criteria

If you look at the overall responses, you can see that the patients who got the vorinostat, which are in yellow, had a better response rate, more complete responses and more very good partial responses than patients who only got bortezomib. That's the good news.

Slide 72: Progression-free Survival

Unfortunately when you look at progression-free survival, you can see that the curves are pretty close together and on average there was less than a one month benefit to the addition of vorinostat with no difference in overall survival.

Slide 73: Adverse Events

If you then look at adverse events, you can see that the group that got bortezomib with vorinostat had a greater likelihood to have low platelet counts and low white blood cell counts, as well as GI complications like diarrhea, as well as nausea and also an increase in fatigue.

So it'll be interesting to see if these data will support approval of vorinostat. My feeling is that with less than a one month benefit, in consideration of the increase in side effects, this will be a difficult combination to get approved by the Food and Drug Administration.

Slide 74: 2011 ASH Abstract 480

However, there was a second study done of vorinostat with bortezomib, but this time it was in patients with bortezomib refractory disease.

Slide 75: IMWG Response Data

And in these patients there was about a 17 percent response rate with a duration of response of about seven months.

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Slide 76: Progression-free Survival
And here you can see progression-free survival was about three months. And because patients whose disease is growing on bortezomib are a difficult group to treat and don't have other options, this may prove to be something to consider.

Slide 77: 2011 ASH Abstract 813
On a more positive note, we have an update on carfilzomib in the relapse setting.

Slide 78: Study Design
And this was a study that focused on patients who had relapsed or refractory disease after one to three prior lines of therapy. And also these were patients who were bortezomib-naive, meaning they had not yet gotten bortezomib.

Slide 79: Carfilzomib Activity
Two different doses of carfilzomib were used, either 20 or 27 milligrams per meter squared, and you can see a good response rate in both, with maybe a higher response rate in the higher dosing group.

Slide 80: Response Durability
Also if you look at response durability, you can see that the time to progression was about eight and a half months for the lower dose group and haven't yet been reached for the higher dose group. And if you remember, bortezomib had about a six and a half months time to progression.

Slide 81: Progression-free Survival
So that would suggest that carfilzomib may be at least as good or possibly even better, and progression-free survival again is shown here, with fairly good numbers overall.

Slide 82: 2011 ASH Abstract 302
I did want to briefly tell you about another proteasome inhibitor, which is also in clinical trials, called marizomib or NPI-0052.

Slide 83: Responses at Full Dose Marizomib ± Dex
I didn't want to spend a lot of time on this because it's still in Phase I studies, but these data do suggest that it also will be active and may be active even in patients who got bortezomib. So it may be that in the future we'll have a panel of proteasome inhibitors to select from, including bortezomib, carfilzomib and marizomib.

Slide 84: 2011 ASH Abstract 812
Another drug class that's quite exciting is pomalidomide, which is another immunomodulatory drug related to lenalidomide and thalidomide. And there were a number of different studies that were presented at ASH.

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Slide 85: Study Design
I wanted to highlight this one, which was from the French, which compared two different ways of giving pomalidomide with dexamethasone. One was to give it like lenalidomide, 21 out of 28 days. The other was to give it like thalidomide, meaning 28 out of 28.

Slide 86: Response Data
You can see that both had a good response rate of about 35 percent and also a good duration of response, which was anywhere from seven months to about ten and a half months.

Slide 87: Time to Events
And if we look at time to events, the time to progression was about nine months with overall survival being about 13 months. And what one would expect in this group is about nine months. So it looks like this drug has good activity and combinations with pomalidomide are being investigated as well. For example, at MD Anderson we have a study of carfilzomib and pomalidomide together because they look like the two best drugs right now in the relapse setting as single agents.

Slide 88: 2011 ASH Abstract 303
A lot of interest has been focused on antibodies for myeloma and probably the first one that will be approved, although we hope it will be a few years off because, unfortunately, the Phase III study is still being started, but nonetheless for elotuzumab we have a Phase II result

Slide 89: Efficacy
and you can see here in terms of efficacy, that elotuzumab with lenalidomide and dexamethasone in the relapsed setting has a 92 percent response rate in that second column at 10 milligrams per kilogram. Median time to response is one month, which means the responses are very rapid, and time to best response is only two months, so a very rapid benefit.

Slide 90: Progression-free Survival
And progression-free survival looks quite good. You can see that the median has not yet been reached and the numbers are getting out to about over a year for progression-free survival, which means overall survival would probably be a couple of years, which is very encouraging.

Slide 91: Adverse Events
And the side effects are very manageable, with only some infusion-related toxicity.

Slide 92: 2011 ASH Abstract 303
Briefly also bendamustine is an interesting drug. I mention this because it is approved in the U.S. and so this is an option now. You don't have to go on a clinical trial to get it.

Robert Z. Orlowski, MD, PhD
December 19, 2011

DR. ROBERT ORLOWSKI:

Slide 93: Study Design
And there was one presentation of bendamustine with lenalidomide and dexamethasone. Bendamustine is IV, but it was given only on two consecutive days of every 28 day cycle, which means that you got the rest of the 26 days to go and do your shopping.

Slide 94: Dose Limiting Toxicities
And what was seen is that the main side effects were a decrease in blood counts

Slide 95: Response Rates
and the overall response rate with that combination was quite good at 52 percent, with almost 90 percent of patients having stable disease or better.

Slide 96: Outline
And then finally I wanted to say a little bit about supportive care.

Slide 97: 2011 ASH Abstract 993
There was a trial presented last year from the British myeloma group, which was updated this year, and one of the important points from the study is shown here,

Slide 98: Trial Design
which is the impact of zoledronic acid.

Slide 99: Impact of Bisphosphonates
And what was seen is that patients who got zoledronic acid for their myeloma, in addition to chemotherapy, lived an average of about five months longer, suggesting that that drug had some effect, not just in helping bone disease, but also some effect against multiple myeloma.

Slide 100: Impact of Maintenace Therapy
And again here, if you look at impact of maintenance therapy, there was some improvement in progression-free survival for patients who got thalidomide maintenance, as opposed to no maintenance.

Slide 101: New Approaches to the Management of Patients with Multiple Myeloma: Summary
So before I go to the questions, let me just sort of summarize my take-home messages from ASH in these different categories.

Slide 102: What Have We Learned?
First of all, for smoldering or asymptomatic myeloma, we can identify patients at high risk of progression. They may benefit from early therapy, like with lenalidomide and dexamethasone. Although this is not yet a standard of care. And we do still have concerns about stem cell collection as well as second cancer. And we need a larger trial to try to validate the earlier studies.

Robert Z. Orlowski, MD, PhD
December 19, 2011

DR. ROBERT ORLOWSKI:

Slide 103: Induction Therapy

For initial therapy in transplant-eligible patients, we know that a better induction regimen prior to transplant improves the outcome after transplant. And the standards of care now are bortezomib and dex or lenalidomide and dex as two drug regimens, and three drug regimens like bortezomib with doxorubicin and dex, or bortezomib with either thalidomide or lenalidomide and dexamethasone. Although in the future we may be using things like carfilzomib with lenalidomide and dex or the Millennium 9708 oral proteasome inhibitor, with lenalidomide and dex. And we still do need to figure out if some patients would benefit more from one of these combinations than another.

Slide 104: Transplant and Maintenance

In terms of transplant, I think that even though we have a lot of novel drugs, transplant is still of great value in myeloma. And autologous transplant remains the standard of care. Also I think increasingly after transplant we'll be doing consolidation as well as maintenance. And although the second primary cancer risk needs further scrutiny, the risk of dying due to myeloma is still much greater, and so I think the benefit of maintenance still outweighs the risk at this point.

Slide 105: Other Pearls

And then for patients who are not eligible for transplant, again earlier use of novel agents does improve outcome. And probably the standards of care here are MPT, MPR with lenalidomide maintenance, as well as MPV, although as you saw, bortezomib and dexamethasone is a good option as well. And once again consolidation and maintenance will be a standard.

Slide 106: Impact of Novel Agents up-front

We are making an impact for patients. You can see here that survival for newly diagnosed patients now is better than it has ever been before, although clearly we would like to improve it further, so that no patients die of myeloma ideally.

Slide 107: Additional News

For those patients who have relapsed or refractory disease, the standards of care are still lenalidomide and dexamethasone, as well as bortezomib with liposomal doxorubicin. And reusing drugs that worked before can be an option as well.

We have a lot of novel drugs. I mentioned vorinostat, the benefits of which are unclear, but there are other drugs in that class that still look exciting, including panobinostat and another drug called ACY1215. And we also have the next generation of proteasome inhibitors as well as IMiDs, including carfilzomib, marizomib and Millennium 9708. And in the IMiD class we have pomalidomide.

Slide 108: Impact of Novel Agents at Relapse

In the relapsed setting as well, patients are living longer and doing better than has ever been the case before.

DR. ROBERT ORLOWSKI:

Slide 109: A Cornucopia of New Drugs
And in general I think we have a great cornucopia of new drugs and it's very important therefore for patients to make sure that they talk with their healthcare providers not just about standard therapy, but about what clinical trials are available. Because often those are the ones that have the most exciting new drugs.

Slide 110: Lymphoma & Myeloma Center
If you are interested in coming, for example, to MD Anderson, here is a little bit of information about our referral line. It's a toll-free number, which is pretty easy to remember. It's 1-855-Myeloma.

Slide 111: Faculty
And we have six faculty who focus on myeloma, and even though some of these photographs are out of date, fortunately our doctors are not out of date when it comes to myeloma therapy. And I did include my email address there. You can feel free to email me with questions. And also my Twitter account is there, for any of those of you who tweet. And then the last link there under my name is the link to our list of available clinical trials.

So again, thank you very much for listening. I'm happy to take questions.

LAUREN BERGER:
Thank you so much, Dr. Orlowski, for sharing so much new information from the ASH conference and really bringing us up to date.

Slide 112: Question and Answer Session
It is now time for the live question and answer portion of our program.

LAUREN BERGER:
We will take the first question from the Web audience and that question is from Joe, who asks how accurate is the M protein count in determining the level of cancer in the marrow?

DR. ROBERT ORLOWSKI:
Joe, thanks very much for that question. The M protein count is one of the most important measurements of myeloma burden, but it's important to know that myeloma can sometimes change and sometimes it goes from a variant that makes an M protein to one that doesn't make an M protein, and therefore you can be fooled because you think that myeloma is getting better, the numbers are going down, but in fact it's because the protein just isn't being made. So it's important therefore to not just follow the M protein in the blood, but also to do what are called serum free light chain measurements in the blood, as well as urine protein measurements. And unfortunately in some cases the bone marrow aspirant and biopsy may still need to be done. We haven't completely gotten rid of the need to be able to do that.

Also in some cases an MRI or a PET scan may be valuable ways to measure the amount of myeloma. And so really all of these put together are ideal in measuring how much disease is present.

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

OPERATOR:
Our next question comes from Jack in California.

JACK:
Terrific presentation and slides. Can you say something about treatment preference for the copies of 1q high risk factor?

DR. ROBERT ORLOWSKI:
Very good question, Jack. So unfortunately I didn't get into this in detail because there was a limited amount of time, but you're bringing up an important point, which is that one of the other high risk abnormalities is so-called amplification or increased number of copies of 1q. And actually one of the presentations I did briefly review, which was from the German and Dutch groups, did suggest that more copies in that area was worse than fewer copies in that area. Unfortunately we're not yet at the point where we know for sure what the best approach is to those high risk patients. There have been varying reports about the activity of bortezomib. Some have suggested that bortezomib overcomes that high risk feature. Other have suggested that it does not. So unfortunately more research will be needed in that area.

LAUREN BERGER:
Thank you for your question, Jack. We'll take the next question from the Web audience and this question is from Mike and Mike asks, please talk about MRD testing for multiple myeloma.

DR. ROBERT ORLOWSKI:
Oh, very good. So Mike, MRD, which for those of you that don't know what that stands for, it's minimal residual disease, right now our most commonly used criteria for response are based on Joe's earlier question about M protein values. But we know that even if your M protein goes to zero, which is certainly a good outcome, nonetheless there is leftover myeloma present.

Probably the two most common ways to measure that, one is by what's called flow immunophenotyping. And basically what that is is that on the bone marrow the plasma cells are looked at and not just what number of plasma cells there are, but the proteins on the surface are looked at. If you will, it's kind of like a fingerprint. Because you can have normal plasma cells in there, which would be good, or you can have myeloma plasma cells, which would be bad. And we can differentiate between them, using this immunophenotyping, so that's one way, which is now fairly routinely available, especially at larger academic centers.

The other approach, which is not yet routinely available, is by so-called PCR, I mentioned this briefly, polymerase chain reaction. That's something that is still research-related, in part because since myeloma patients have different types of disease, we don't yet have one test that measures all the different types.

So right now your best bet for MRD testing is with a bone marrow and immunophenotyping of the plasma cells.

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

OPERATOR:
Our next question comes from Norma in California.

NORMA:
Should we be using the term remission at all? I hear the two terms remission and response used by, I think less informed patients interchangeably. Of course, they're not interchangeable. But with this disease, where there is not yet anything agreed upon as a cure, should we be using remission?

DR. ROBERT ORLOWSKI:
That's a good question, Norma, and unfortunately sometimes those terms are used by less informed doctors as well. I think that it's a little bit of a question about what people understand about the term remission. If the term remission means to some people cure, then I agree with you that we shouldn't be using the term remission because, unfortunately, remission is not the same as a cure. As I mentioned earlier, we do know that there are still a fair amount of myeloma left, even in patients who are in complete remission.

However, I do think that that term is useful because a complete remission is certainly better in most cases, especially if you are able to maintain the complete remission for a long time, than patients who have only a partial remission, which means at least a 50 percent reduction.

So I think that as long as people understand that remission is not the same as cure, I think it's still a worthwhile measure, especially if it's a complete remission.

LAUREN BERGER:
Thank you for your question, Norma. We'll take the next question from the Web and this question is asked by Stuart. With regard to bortezomib, what is the current data on subcutaneous administration of Velcade®? And why is the risk of local reactions greater it seems than the initial 6 percent?

DR. ROBERT ORLOWSKI:
A good question, Stuart. You know probably that especially at last year's ASH meeting, and these data have now been published, the French presented a study in patients with relapsed myeloma, that compared the intravenous bortezomib with subcutaneous bortezomib. And what they found was that the outcomes were basically identical, which is a good thing. And even better was the fact that the group that got subcutaneous bortezomib were less likely to develop neuropathy. The number still didn't go to zero, we'd like it to be zero percent neuropathy, but they certainly were significantly better. And also to some extent, it can be more convenient for patients because instead of coming in and having to have an IV placed and then have it removed, you could just get an injection of the bortezomib underneath the skin.

You are right that there is a risk for local reaction. So far they've typically been described as being transient and not recurrent and it seems like the risk of patients needing to have the subcutaneous dosing discontinued is relatively low. As to why the reactions are maybe a little bit higher than what has been reported, my guess

DR. ROBERT ORLOWSKI:
would be that it's probably just a factor of people needing to learn a new approach to therapy and as with other things, the first couple of times that you do it, you may not be as good at it. And hopefully when people have more experience, the experience in the community will be similar in terms of reactions to what's been published.

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

OPERATOR:
Our next question comes from Mary in Florida.

MARY:
It has to do with the protein measurement. I have oligosecretory. My protein always hovers at 5.7 and on my lab sheet it says that's low. I thought you mentioned 3 grams being high. I'm a little confused.

DR. ROBERT ORLOWSKI:
Thanks, Mary. For folks that have oligosecretory disease, what that means is that your myeloma makes a very small amount of protein and therefore it may be difficult to exactly measure how much disease you have, based just on the protein level. So you're probably in that category that I described earlier to Joe's question about measuring the M protein in the category of patients who could benefit not just from the M protein measurement, but from measurement of the serum free light chain level, that's the free-kappa, the free-lambda and the kappa to lambda ratio. In some cases it may be helpful to do Bence-Jones protein levels in the urine. And a PET scan may be helpful as well. And ultimately it may be that you will need a bone marrow, although hopefully with these other tests that could be avoided.

LAUREN BERGER:
Thank you for your question, Mary. We'll take the next question from the Web audience and this one is asked by James. James says I'm a 77 year old multiple myeloma patient. The drug Doxil® is recommended for my next treatment. I have been told that Velcade and Revlimid® are no longer an option since I had a bad reaction to both. I have a weak heart and four stents in place. I would like your opinion on the risks involved with Doxil as I have been told that patients with a heart condition are at greater risk when taking Doxil. Is there a third alternative?

DR. ROBERT ORLOWSKI:
James, thanks for your question, I'm sorry you're faced with this situation. Part of the answer will depend, I think, on what reactions you had previously to bortezomib and also lenalidomide. If they were very severe reactions, then it may very well be that you should not go back to those drugs. But if the reactions were mild and manageable, sometimes you can combine the bortezomib and lenalidomide together and they will work, even if separately before they did not.

DR. ROBERT ORLOWSKI:

Another option may be to consider using thalidomide because that can be active even in patients whose disease has not responded to bortezomib or to lenalidomide. And also you could think about, for example, cyclophosphamide or melphalan or even bendamustine, which are so-called alkylating agents.

As to Doxil or pegylated liposomal doxorubicin, we know that that drug is much less cardiac toxic than regular doxorubicin. A couple of years ago we did a study of bortezomib compared to bortezomib with liposomal doxorubicin and we found no significant increase in heart problems with the combination than with bortezomib alone. So I think that in general I could say that, as I mentioned, Doxil is more cardiac safe. But it sounds like you do have a significant heart history and without knowing more detail, it would be difficult for me to be completely comfortable recommending that you do it. And again I would think about thalidomide or maybe one of the alkylating agents, along with steroids. And it may be, as I mentioned earlier, that you would be somebody who would be a candidate for a clinical trial, such as a trial with maybe carfilzomib or a trial with pomalidomide, and those drugs also have a low risk of heart side effects.

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

OPERATOR:
Our next question comes from Pat in Pennsylvania.

PAT:
Thank you for your presentation, Doctor. Five and a half years ago I had an autologous transplant, but now my numbers are beginning to go up, they're up in the 500s. I had a PET scan which proved okay. Would you recommend another transplant, maybe an allogeneic this time? Now with the other transplant I had C. diff, the following months, for three months. So could you give me your advice?

DR. ROBERT ORLOWSKI:
Sure, thanks, Pat. First of all, it's always difficult to give advice on very specific cases without having the opportunity to review the records and also see the patient in person, so I'm going to give you that disclaimer. And of course, we'd be happy to see you down here and it's probably a little bit warmer here in Houston than it is up there in Pennsylvania this time of year.

Now in terms of your particular case, I think that since you had a very good benefit with the autologous transplant from the perspective of having gone five and a half years before relapsing, you would be in the category of patients who would be good candidates for a second autologous transplant. As I showed you in the slides, your benefit with a second transplant might not be quite as long, but on the other hand, if you add maintenance therapy, which you may not have gotten before, it could be the same or even longer.

I wasn't able, because of time constraints, to show you another study that was reported, which compared the benefit of an autologous versus a mini-allogeneic transplant. And the conclusion of that study was that the autologous second transplant was a better way to go because of the risk of complications with the so-called mini-allogeneic transplant.

DR. ROBERT ORLOWSKI:

So again it's tough to do something specific for you as an individual, but in general it sounds like a second auto would be a better option for someone like you, than a mini-allo. And although you did have C. diff the first time and you could again have it the second time, that's not by any means guaranteed, and hopefully you would sail through more smoothly this time.

LAUREN BERGER:
Thank you for your question, Pat. We'll take the next question from the Web audience and this question is from Janice and she asks, can you offer some explanation of why the serum M spike and the urine M spike show at varying levels? With the serum M spike coming down, but the urine M spike remains high.

DR. ROBERT ORLOWSKI:
Thanks for your question, Janice. I think that a lot of that can be dependent on the biology of the myeloma. I did mention earlier that sometimes the myeloma changes from a variant that makes an M protein, to one that sometimes doesn't make an M protein. And we also do see something called light chain escape, which again is sort of similar, but instead of making a full M protein, you can start making light chains only. Also in some patients it looks like they can have two different types of myeloma, one that can make an M protein and one that only makes the light chain. And it's possible that that's the situation in your case. So I would say that if the serum M protein is coming down, but the urine light chains are going up, unless the increase in urine light chains is small, because there's always some variability, I would say if the increase in urine light chain is large, that that is concerning for the possibility that you have one of these escapes, where the myeloma is in fact progressing, and I would encourage you to do some of the things we've talked about earlier, including maybe a bone marrow and maybe a PET scan, to try to see what's going on, because it could be that you need to do a different therapy than you're on now.

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

OPERATOR:
Our next question comes from Richard in New Jersey. Please state your question.

RICHARD:
Hello, Doctor. I'm being treated at the John Theurer Cancer Center at Hackensack University Medical Center. I recently relapsed after two years after an autologous stem cell transplant and before that I was on Revlimid with dex and I did the whole nine yards, and now I'm at a point where I have a choice of three different treatments, either to do another stem cell transplant with the same drugs I used three years ago, or using my brother's stem cells, or going into a clinical trial for carfilzomib. And I'm kind of leaning toward the clinical trial because my doctor at this point still is at a wait and see attitude because my readings are still fairly low. My cancer is progressing back very slowly. So I'm kind of thinking about the third option, the clinical trial. I was wondering what you thought about that.

DR. ROBERT ORLOWSKI:
Thanks, Rich, for your question. I know some of the folks over at your cancer center and you're in good hands there, so that's good news. I think a lot of the discussion we've had earlier would apply here. It's tough to say on an individual basis, but in general the data suggests that if you're considering a second transplant, that you're better off with an autologous transplant as opposed to a mini-allogeneic transplant, especially in terms of outcome and also in terms of side effects and toxicity. So that's one thing to say.

The second thing in terms of clinical trials, carfilzomib is certainly a drug that can be well tolerated and that some people have been on for quite a long period of time. Depending on the type of myeloma that you have, it may be therefore appropriate to think about a trial.

And lastly I think what you alluded to is important. Just because the numbers are going up doesn't necessarily mean that you automatically need to get treatment. As long as the numbers are at a relatively modest level and there's no evidence of any end-organ damage, I think that it may be very reasonable to watch and wait for some period of time, as long as the disease is not doing anything bad to your body.

LAUREN BERGER:
Thank you for your question, Richard. We'll take the next question from the Web audience and this question is from Roger and he asks should all post-stem cell transplant lenalidomide maintenance therapies include low dose dexamethasone?

DR. ROBERT ORLOWSKI:
Thanks for your question, Roger. It's a very good question because lenalidomide is usually used with dexamethasone, either in the newly diagnosed setting or in the relapsed setting. But in the maintenance setting it's not. The reason for that is that all of the trials that so far have been done, the really good large studies used lenalidomide as a single agent. The rationale for that is a few things. First of all, with long term dexamethasone, people do worry about the risk of infections, possibly decreasing bone density and even of developing diabetes. And also lenalidomide is thought to work in part by so-called immunomodulatory effects, which mean that in part it may stimulate the immune system and because steroids suppress the immune system, they may actually reduce that benefit.

So right now the standard of care is just to do lenalidomide by itself and I don't add dexamethasone to patients getting lenalidomide maintenance unless their numbers start to go up on lenalidomide alone, or if they have some side effect to lenalidomide that I think would be helped with a little bit of dex.

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

OPERATOR:
Our next question comes from Judith in New Jersey.

JUDITH:
I'm a myeloma patient who had my transplant in January of this year and I was not placed on maintenance therapy. And I've noticed now that as of late the numbers, the light chains, seems to be going up slightly, with 3.0 in July and 7.3 in October. So I'm just wondering have I relapsed or should I consider at this point some kind of maintenance therapy. And I'm on a watch and wait kind of protocol at this time. Thank you.

DR. ROBERT ORLOWSKI:
Thanks for your question, Judith. The laboratories for the free light chains are sometimes done in different places and so I think it's important to know what the normal range for your laboratory is. But I think a rise of the type you're describing could indicate one of two things. One thing is it could be increasing myeloma disease burden. The other thing is that after transplant it can take a little while for the normal immune system to start to come back and it could be that that rise in numbers is just an indication of your immune system returning to full health. So what would be helpful to know would be, and maybe you can email me this, again my address is on the slide, email me the ratios, the kappa:lambda ratios and how those have changed. But my general answer to your statement is that lenalidomide probably is helpful in all patients after transplant. And I do try to recommend maintenance with lenalidomide to all of my transplant patients unless they've been on lenalidomide before and had some kind of really bad reaction. Even patients in complete remission after transplant do seem to benefit from lenalidomide maintenance. So I think that's my best answer to your question and feel free to follow up with me by email.

LAUREN BERGER:
Thanks for your question, Judith. We'll take the next question from the Web audience and this question is from Peter and Peter asks what is the vaccine that you referred to after transplant?

DR. ROBERT ORLOWSKI:
Thanks, Peter. So the vaccine is a combination of approaches, but one of them is to do a vaccine against the so-called M protein. You may know that the M protein, which is made by the myeloma cells, is a protein that is unique. There's no other protein like that in the body and the idea is to collect some of that M protein before the transplant and use it to generate a vaccine response after transplant. And we're also collaborating on that study with Dr. Carl June at the University of Pennsylvania. Some of you may have read about some of his recent work using T cells against chronic lymphocytic leukemia. And so what we're doing is we're combining the vaccine against the myeloma M protein with his activated T cell technology, to try to further reduce the amount of myeloma that's present after the transplant.

Now what that means is that we do need to be able to collect some of the M protein from each patient's blood, then do the transplant and then do the vaccine. So if you've already had your transplant, that probably wouldn't be something that we'd be able to do. But if you're interested again, feel free to contact me and I can put you in touch with the people who would be able to screen you, as it were, to at least let you know whether you would be eligible and therefore whether you should come down here for an evaluation or not.

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

OPERATOR:
Our next question comes from Connie in Florida.

CONNIE:
Actually I think they just answered mine, too. I was concerned about the vaccine. I had my transplant already and I don't know if they had taken any M protein, so I'll check with Moffitt and see if that was done or not.

DR. ROBERT ORLOWSKI:
Yeah, it can be done on stored protein, but the amount that is required is fairly substantial. So we'd need more than one or two tubes. So this is really probably an approach that's best for people that haven't yet had their transplant. But do think about maintenance therapy as I mentioned earlier because the less myeloma you have, the better, of course.

LAUREN BERGER:
Thank you for your question. We'll take the next question from the Web audience and this one is from Richard. Are there any new treatments for patients who develop leptomeningeal myelomatosis?

DR. ROBERT ORLOWSKI:
Good question, Richard. For those of you that don't know, leptomeningeal myelomatosis is a condition where the myeloma cells get into the cerebrospinal fluid or brain area and, of course, don't do very good things there. Right now, fortunately, this is a relatively rare complication and tends to happen only with very advanced disease. Unfortunately, when it does occur, the options for treatment are less robust because the chemotherapy drugs that we give IV don't penetrate well through what's called the blood-brain barrier and those drugs therefore don't get into the areas where the leptomeningeal disease is present. So right now the best approaches are still to do things like radiation or other drugs that we use for leptomeningeal cancer of other causes, which can include drugs like thiotepa or methotrexate or cytarabine. But you're right, we do need to do a better job in that area. And fortunately some of the new drugs that are coming through are better at penetrating into the central nervous system, so hopefully they will be of greater benefit for patients with that complication.

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

OPERATOR:
Our next question comes from Carol in New York.

CAROL:
I'm a multiple myeloma patient and went through – hoping to go through a stem cell transplant, autologous. And turns out that I am ineligible. My induction therapy was Velcade, Revlimid and dexamethasone. Took me 12 cycles to get to a point where they were hoping to collect my stem cells and move me into transplant.

CAROL:

Turned out that in that process of waiting to get my stem cells harvested, that I relapsed and then went under two cycles of DCEP treatment, which my numbers came down, although I still had 40 percent myeloma in my bone marrow, so was unable to follow through with transplant. And now I'm on Revlimid, just 15 mgs, and I'm showing that – I'm remaining pretty stable. So I'm just wondering, I'm 53 years old, and I'm wondering about if there possibly is a chance of being able to be stem cell transplant eligible,n again, with getting numbers down.

DR. ROBERT ORLOWSKI:
Carol, a quick question before you sign off. So you've not yet had your stem cells collected, is that right?

CAROL:
That's right.

DR. ROBERT ORLOWSKI:
Thanks very much for your phone call and again I'm sorry that you're in that situation. It does seem that the less myeloma people have at the time that they get their transplant, the better the outcome. So having 40 percent still in the bone marrow is quite a bit and would reduce the likelihood of a long term benefit. But you mentioned some of therapies that you've been on and there are others that could be considered, that might be helpful in reducing the disease burden. And a lot of those are a little bit similar to DCEP, there's the combination called DTPACE, which is similar to DCEP, but has a few other drugs, and that might be an option for you. It also may be possible to do something with a novel drug like pomalidomide or carfilzomib, to bring your plasma cell counts down to the point that the collection will be easier to do.

LAUREN BERGER:
Thank you for your question, Carol. We'll take the next question from the Web audience and this is from Janice and she asks why does myeloma come back hard?

DR. ROBERT ORLOWSKI:
Thanks, Janice, for that question. Myeloma can be different. In some patients when the myeloma relapses it actually is very indolent and sometimes you have a low level M protein that just stays there for a long time and nothing may need to be done. Unfortunately in many patients, you're right, that it comes back more aggressive. And part of the reason for that is that by treating with chemotherapy, what we're doing is we're killing the cells that are sensitive, but just by blind dumb luck there are often a few cells in there that are heartier and resistant and they're the ones that survive therapy and then start growing, so that when you relapse the cells that have come back are more aggressive and more difficult to treat. We do need more studies to understand the mechanisms of drug resistance. We're actually interested in that ourselves and have a number of projects in that area. If we could identify why myeloma cells become resistant, we could suppress that and improve the efficacy of our chemotherapy.

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

OPERATOR:
Our next question comes from Kate in North Carolina.

KATE:
My husband was diagnosed with multiple myeloma in June and he's 45 years old and we're getting treated at Duke University, and he's going in for, he's going to do a treatment of Cytoxan® in two weeks and then Neupogen® and then they're going to harvest his stem cells the following week, the week of January 9. And my question basically is he's on a clinical trial and the trial calls for waiting to do the actual transplant until progression and I was just wondering what your school of thought was on waiting until progression. He is in remission. And I was just wondering what your thoughts were on doing it during remission or doing it at progression.

DR. ROBERT ORLOWSKI:
Kate, thanks for your question. You're part, as you said, your husband is part of a clinical trial and clinical trials are important because those are basically the tools that we use to try to learn about such questions. I think the folks at Duke I know very well because before being at MD Anderson I was over at UNC in Chapel Hill, so you're in good hands. Because one of the hats that I wear is that of a researcher, I have to say that we always encourage patients to try to stay on clinical trials. That having been said, if you ask my opinion, there's a couple of things.

We do know from years ago when studies were done, looking at early transplant versus doing transplant at the time of first relapse, that the outcome was no different, which would suggest that it is perfectly safe to wait until the disease relapses before going on to stem cell transplant. So that would argue in favor of what your husband is doing.

However, those studies were done at a time when the chemotherapy drugs that we used were much less effective and the difference between early and so-called late transplant was only about six months on average. So we don't know with our better drugs, right now, what the true story is. There is an ongoing trial, and maybe this is the trial that he's a part of, which is being done with the French and a number of centers here in America, which is looking at bortezomib, lenalidomide and dexamethasone and then early versus late transplant.

Off of a protocol, my inclination is to think that myeloma cells are most sensitive at the beginning and once the disease relapses it becomes a little bit more difficult to treat. So this is now my patient advocate hat. And what I would say is that although we don't have data to be sure, my bias is that early transplant is probably better than later transplant.

So unfortunately, I gave you kind of two opinions there and I apologize. But right now the data would suggest that the delayed transplant is safe and effective.

Slide 113: LLS Resources (1:29:39)

LAUREN BERGER:
Thank you for your question, Kate, and we wish your husband the best. And thank you all for all of your questions. Our program has come to a close. Please help me thank Dr. Orlowski for donating his time today. We hope that many of your questions were answered and that the information will assist you in your next steps. If we were not able to get to your question today or we can provide additional information or support, please call an Information Specialist at The Leukemia & Lymphoma Society toll-free at 800-955-4572.

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

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