Welcome and Introduction

Carson Jacobi, MPH

Hello everyone, good afternoon and good morning wherever you are. Thank you so much for joining us today on our program. On behalf of *The Leukemia & Lymphoma Society*, we thank you for choosing to spend this hour and a half with us today.

My name is Carson Jacobi, MPH, and I'm the Vice President of National Education Programs for *The Leukemia & Lymphoma Society*.

We welcome you to the program today, “Emerging Therapies in Leukemia, Lymphoma & Myeloma” featuring Dr. Gail Roboz, Dr. John Leonard, and Dr. Robert Orlowski. We thank them all for sharing their time and expertise with us today and for their ongoing dedication to serving families touched by cancer. We also would like to acknowledge and thank Celgene for their support of today’s program.

You all should have received a packet, including an agenda, a biography of our 3 speakers, and an order form for *The Leukemia & Lymphoma Society’s* materials, and we do encourage you to look through all the materials at your leisure if you have not already done so.

You’ll also find an evaluation form for you to fill out for today’s program, and if you are a nurse or social worker, you can receive 1.5 hours of continuing education credit and there is a form specifically marked for you in the packet.

After our presentations, we will open up to questions from all of you, our telephone audience, and we do have about 1200 people registered for our program today from across the United States and we do have some international participants.

If we are not able to get to your questions today, you can reach out to our Information Resource Center, which we refer to as the IRC, and the toll-free number is included in your packet, but I will mention it now. It’s 1-800-955-4572. This will connect you with an oncology professional who can answer your questions, help you obtain information, or order free materials specific to your needs. The IRC’s hours are 9:00 AM to 6:00 PM Eastern Time, Monday through Friday.

Also, we’d like you to know that we are audiotaping and transcribing today’s program for posting on the LLS Web site in several weeks. This provides an opportunity for you to read and to listen again to today’s presentation, especially to follow up on terminology or therapies that you may have missed.

And before I turn the program over to our first speaker, I would like to introduce *The Leukemia & Lymphoma Society’s* President and CEO, John Walter, who is on the call today to welcome you and share a few words with you.

John, thanks for joining us.

John Walter

Thank you, Carson. I’d like to add my welcome to all the patients, caregivers, and healthcare professionals on the call today. We are very fortunate to have as our presenters today 3 individuals who have dedicated their careers to improving the lives of cancer survivors and their families. Drs. Gail Roboz, John Leonard,

and Robert Orlowski are experts in leukemia, lymphoma, and myeloma. We appreciate their dedication to supporting the mission of *The Leukemia & Lymphoma Society* through their research and their work everyday with patients and their families. I wish to thank each of them for taking the time out of their busy schedule to help further your understanding of emerging therapies.

The Leukemia & Lymphoma Society is committed to bringing you the most up-to-date information about blood cancers. 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 its founding in 1949, the LLS has invested more than $600 million for 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.

We hope this teleconference will be helpful to you on your journey forward. Thank you and I'll turn the program back over to Carson.

Carson Jacobi, MPH

Thanks so much, John. I now have the pleasure of briefly introducing each of our speakers and then Dr. Roboz will start the program off for us.

Dr. Gail Roboz is the Associate Professor of Medicine and the Director of the Leukemia Program at the Weill Medical College of Cornell University/New York-Presbyterian Hospital in New York City, and Dr. Roboz will talk to us today about the “New Developments in Leukemia Treatment.”

Then, we have Dr. John Leonard, who is the Richard T. Silver Distinguished Professor of Hematology and Medical Oncology and the Professor of Medicine at the Weill Medical College of Cornell University/New York-Presbyterian Hospital in New York City, and he will talk to us about “Evolving Therapies in Lymphoma.”

And then we have Dr. Robert Orlowski. Dr. Orlowski is an Associate Professor in the Department of Lymphoma, Myeloma, and Experimental Therapeutics in the Division of Cancer Medicine at The University of Texas, MD Anderson Cancer Center in Houston, Texas, and Dr. Orlowski will talk to us about “New Strategies in Myeloma Treatment.”

We’re thrilled to have all 3 of them with us today. Dr. Roboz, I'll now turn the program over to you.

New Developments in Leukemia Treatment

Gail J. Roboz, MD

Thank you for the invitation to participate in the call and I have been given a pretty giant task today of covering leukemias.

Now leukemias, as a lot of people on the call surely know, cover a lot of diseases. So there are acute leukemias–acute myeloid leukemia, acute lymphoid leukemia. There are chronic leukemias–chronic lymphocytic leukemia, chronic myeloid leukemia. There are also subtypes of the leukemias that are quite rare. For example, large granular lymphocytic leukemia or hairy cell leukemia.

And I think just from the list, and from the alphabet soup that I have just started describing, it should become quite clear that it's a pretty giant task to go through all of them. So in preparation, actually, for the call, I decided to pretend that I was trying to find something out about clinical trials in leukemias and I logged on to www.clinicaltrials.gov and then there was a prompt that said, "Search for clinical trials." So I did that and I got a tab that asked me to type in what I was looking for and I typed in, "acute myeloid leukemia," and I got 1139 trials.

And I think that, as a patient or a caregiver or even a healthcare provider, trying to look out for a patient, there are several potentially different interpretations of this 1139 that pops out of Google. One, if you're in an optimistic mood, you can say, "Wow! This is amazing. There's so much research going on, how fantastic, what an incredible number of options." But I think that equally likely might be a reaction of, "Oh my God! Nobody knows what they're doing. How am I going to possibly figure out from which of these trials to choose?" And I only told you about the AML trials. There were more than 900 ALL trials, 1198 for CLL, and 866 for CML. And I pulled these up yesterday and if you go today, there are going to be more.

And, furthermore, if you're trapped in some of the naming problems and you pull up acute myelogenous leukemia, for example, instead of acute myeloid leukemia, even though they're the same thing, they come up with different numbers. So I think, in summary, it can be a very, very overwhelming experience.

Furthermore, what you'll also see when you jump onto the Web sites is that you'll get things like recruiting, not yet recruiting, completed, not completed; and I think what starts happening is that you start wondering what is going on with all of these trials, "How do I know which ones are good? How do I know which ones are going to be the ones for me? How do I know if I'm even eligible for a trial?" And part of our work today is to take a small crack at some of these big questions.

So the first thing is, for all of my patients with leukemia and team out there, everybody with a diagnosis of leukemia can certainly think about a clinical trial because while I would love to be on the phone telling you that the research and the progress in leukemia is so fantastic that the treatment algorithms are so clear and perfect that nobody needs a clinical trial, that isn't true; and although there have certainly been major and important accomplishments and we're definitely farther along with many of these diseases than we were even just a few years ago, it is absolutely correct to say that anybody with a diagnosis of leukemia can at

least be interested in figuring out what is new for them that might be an important cutting edge to know about.

And I want to divide up the leukemias into their subcategories because they're, of course, very different. In talking initially about acute myeloid leukemia, or AML, this disease actually is generally divided into patients who are older than 60 years old and patients who are younger than 60 years old; and I'm not going to talk about children's leukemias at all on the conference call today.

Now, this distinction for AML is incredibly arbitrary and currently controversial because it used to be that clinical trials were set up to try to divide the so-called younger from the so-called older patients, but it really is very, very clear to most of us that there are 65-year-old patients in absolutely perfect condition who are exercising regularly and in wonderful shape, and there are 65-year-old patients who might have had multiple medical problems or issues, or taking a lot of medicines, for whom additional therapy might be much more challenging.

And I think the fact that age has become such an almost irrelevant consideration numerically but, yet, a relevant consideration in terms of eligibility for clinical trials is very, very important to patients and their families because what you'll find is that there are trials that are labeled for elderly patients or for older patients or for quote "less fit" patients with AML, and this is something that's going to require a lot of discussion with your doctor and the caregiver team to try to figure out whether or not you actually fit into one of these categories.

For patients under 60 with AML, the general plan of treatment is going to be to try to categorize the disease as carefully as possible upfront with information called cytogenetics or chromosomes, information called immunophenotype, and also some molecular characterization of the disease to try to figure out whether or not chemotherapy alone is likely to be curative, or might we want to combine chemotherapy with transplant or other modalities of treatment to try to improve the cure rates.

And this is point one about clinical trials that a lot of people assume that clinical trials necessarily mean an investigational drug. They don't. A clinical trial can include a combination of medications that are already approved and commercially available, it can include dose changes and ways that we usually give treatment, it can include stem cell transplantation, it can include a lot of different things, which is why I reiterate my statement from the beginning that all patients with leukemia can definitely think about clinical trials because it doesn't necessarily mean you're getting a completely novel drug or even a completely novel therapy. There might just be a tweaking of an existing therapy that could be relevant for you.

For the younger patients, younger than 60 years old, we're going to make an effort to strategize upfront for whom transplant will be an important option. Sometimes that decision is actually pretty straightforward, sometimes it's not at all straightforward; and the data can even be frustrating to try to figure out whether a transplant is really the way to go. But that is something that's going to be done very early as part of the treatment plan and what younger patients with AML will find when they go onto the Web sites is that there are trials that are designed not only for brand new diagnoses, but also for patients who are already in remission, what happens after they're in remission. Do they get more chemotherapy, do they get something else to try to keep the disease in remission? And, also, trials for what happens if the disease comes back after chemotherapy or, ultimately, for some patients, after transplant therapy.

So, the divisions that you're going to find when you go through the Web sites are going to be sometimes termed induction, or the first treatment that you get for a newly diagnosed disease; consolidation, what kind of therapy are you going to need after you get into remission to try to hang onto a remission, and that would include sometimes stem cell transplant as part of consolidation. And then you may also see some trials that include maintenance, or what type of ongoing therapy might be a possibility for patients who have achieved remission but who are at a high risk of having the disease come back again.

For patients who are older than 60, there are even more decisions than what I've just described because for some of those patients, stem cell transplant is absolutely a consideration and I can say that clinical trials of various transplant protocols of all different kinds of transplants for patients up to the age of even 75 years old are absolutely out there. So, again, nobody is too young, nobody is too old to consider a clinical trial, and in this situation, even a transplant trial might be important for some particularly well patients who have aggressive disease that is diagnosed over 60.

Once again, patients over 60 are going to see the categories divided into induction type of treatment, consolidation type of treatment, maintenance, and then also relapsed or refractory treatments. And the relapsed and refractory ones are sometimes put together and really meaning disease that hasn't responded to the treatment that's been given upfront.

I think for the older patients a particular challenge is to decide on the intensity of the treatment and, here, this is where a lot of discussion is really, really important because the intensity of the treatment is important but so is intensity of the disease. And this is something that often gets overlooked, that just because a treatment may seem like it's very simple and straightforward, leukemia, especially AML in a patient over 60 is very rarely simple and straightforward. So one has to be analyzing not only what does the treatment plan look like, but what does it really mean for me? What does it mean for day-to-day life? What does it mean, not only for the success rates, but also for just the feasibility of going through the program?

That is an easy segue for me to another comment, which is that there's a misconception that participation in a clinical trial is necessarily more cumbersome or difficult or challenging than participation in a standard therapy. For the entire team out there, please know that's absolutely not the case. Just because you're participating in a trial, doesn't mean that there is necessarily anything that's additionally more cumbersome or more difficult and, in fact, some patients find that having the structure of participating in a trial can be very reassuring. So, just to get that note in there.

Switching over for a minute to ALL, or acute lymphocytic leukemia or acute lymphoblastic leukemia, and I can tell you that ALL has naming issues that can drive all of our fellows crazy to try to learn, this is a disease that has had enormous, enormous progress in children, and our ability to get ALL cured in children is dramatically better than it was many years ago. But, unfortunately, that has not translated into corresponding improvements for adults and it is still a difficult and challenging disease for adults.

Once again, similarly to AML, there are for the patients younger than 60 years old almost always upfront considerations of whether or not to undergo a stem cell transplant, and many of the clinical trials that are available are currently still trying to address the unanswered question of for whom exactly, among the ALL patients, is transplant upfront in first remission the best way to go.

And this is a controversial question and part of the reason why there are many clinical trials that are available and encouraged for newly diagnosed patients with ALL is that for a lot of those patients we don't know, even if you put me up against a wall and beg, we don't absolutely know for sure who's going to benefit from transplant in some situations. And clinical trials are actually ongoing to try to answer this question and there have been some recently published clinical trials, which are helping us to understand a little bit better who should go to upfront transplantation. Just, again, arguing for the importance and how grateful we are to the patients who are on those previous trials so that we at least are a little bit better informed.

Now, ALL is a little bit different in that it is common to have a maintenance type of treatment or ongoing lower dose chemotherapy on a daily basis for longer periods of time. That works, actually, in improving survival in ALL. It's less clear in AML, but that is something that you're going to see when you look up clinical trials in these areas that, well, if the disease has a high chance of coming back, what can we do in the long term that's not too brutal for life because you want to be enjoying life in remission, but that might work in preventing the disease from coming back. And that is an area that you're going to see in some institutions in the clinical trials that they will offer.

Because we have international participants and participants from all over the country, these remarks are covering what's available globally. It's, obviously, an important consideration for each patient what is going to be available for them nearby. And I just want to get in as a quick statement early that if we all knew exactly what was the best thing to do in these leukemias, we'd surely all be doing it. The leukemia community is quite close knit, actually, even as an international community, and I think that the things that are hot and that are working well get disseminated and moved along quite quickly for everyone. So, I don't want it to be totally overwhelming that you might actually go to one part of the country and get one recommendation for a trial and then go somewhere else and get another recommendation. Although that can be stressful and frustrating, it's not necessarily bad or indicative of one place having better than the other. It's just showing that there are a lot of things that are still being worked on as contenders for the next hot seat.

Now speaking of what's hot, CML is definitely the area among the leukemias that is the hottest in terms of having effective therapy that, in the last several years, has truly, truly moved forward at wonderful speed. And I can tell you though it's not solved yet because, as you may remember from my earlier comment, when I looked this up there were 866 trials ongoing. So, although many of us know, even from the *Wall Street Journal* that CML is a disease where tremendous progress has been made, patients know that there are still many unanswered questions; and within CML there are lots of different areas that are currently undergoing clinical trials.

For example, if I'm doing well and my oral therapy is working fine and everything looks great, do I need to stay on it? Well, how long do I need to stay on it? Do I need to stay on it forever? We'd love to be able to answer this for patients and there are patients currently participating in long-term studies to try to answer those questions so that we're giving the Goldilocks' approach to therapy. We don't want to give too much and we don't' want to give too little.

Similarly, now that we are so fortunate to have 3 approved agents, well, which one do we use first and do you alternate between them, and is there any point in rotating them? These are incredibly, incredibly important questions and there's a lot of science supporting the belief that maybe some, either changing of

therapies midway or rotation of them or stopping and starting, none of which I'm advocating by the way, but all of which are questions that we want to know the answers to. These are being looked at in clinical trials.

Similarly, for patients who are not responding to one therapy, how do we decide which one to give next? Again, there are clinical trials addressing this. And, then, there are certainly investigational agents available for patients who are not able to get the disease under control with what's available commercially. So, again, CML has great news going on, but we have definitely not "put a period at the end of the sentence" yet.

Now, for CLL, or chronic lymphoid leukemia or chronic lymphocytic leukemia, 1198 trials came up and, again, these were in various stages of recruiting, not yet recruiting, and completed, but just to show you the overall volume of what is out there. CLL is a disease that can last many, many years for patients, and patients may go through different stages where they have active disease and then get a treatment and then they're okay for a while and then it comes back again. And there's really been an incredible number of exciting new agents both being considered alone and also being incorporated into existing regimens that are out there for patients to think about.

One of the most important questions for newly diagnosed patients with CLL in whom the disease might be found on a routine blood test with absolutely no symptoms, is do I need any treatment at all or should I wait until things get worse? And there are definitely clinical trials that are attempting to follow patients long term and ask those questions as well, what if we, we can't split a person in half, but we could split a group in half and see well, what if we treat this group and don't treat the other group, who's going to do better.

Now, if I were a patient, I would just want to know the answer, not necessarily go through the process, but, unfortunately, we have to go through the process and sometimes we're able to learn things on clinical trials faster than we think. And even though we sometimes think it might take years before a question is answered, sometimes, actually, the results become clear much sooner than that. So, especially for patients with CLL who are not sure whether or not to do treatment, or for whom there might be a lower intensity or a higher intensity upfront treatment plan, that's an area where they might be very interested to look into what clinical trials are available.

And I think we are heading right into about 12:28 PM on my clock, so I want to turn it over to John Leonard, MD, to make sure that we stay on schedule.

Evolving Therapies in Lymphoma

John P. Leonard, MD

Thank you very much, and I would like to also express my appreciation for the opportunity to speak today. As Dr. Roboz mentioned, it is a bit challenging to cover a large amount of material in just over 20 minutes or so, but we'll try to hit the high points over the next few minutes.

So, my task is to cover lymphomas and what's new in lymphomas. And one of the challenges, those of you who are dealing with lymphoma either in yourself, or a friend or loved one, is the fact that there are so many different types of lymphoma. And, in fact, within the last year or so, the classification of lymphoma has changed and we now have 60 types of lymphoma. It's not that more types have come out of the woodwork, but it's that we're learning more precisely in a group of patients that were once thought to have the same type of lymphoma now are found to have different types of lymphoma because we're subclassifying and subgrouping lymphomas as we learn more about the biology of the disease, and as far as the prognosis and best therapy for individual groups of patients.

So, there is a lot on the landscape for lymphoma and, in fact, many of the less common types of lymphoma have, in recent years, and in the coming years, drugs that it turns out may be specifically useful for these small groups of patients with these less common types. So I think one thing to keep in mind is that just because someone is dealing with an unusual type of lymphoma, doesn't mean that people aren't working on it. In fact, there are people working on every type of lymphoma and, in fact, there are some new drugs and new treatments and new knowledge that's being gained in really every type of lymphoma that I can think of certainly.

So, we can divide lymphomas in many different ways. They're divided into Hodgkin and non-Hodgkin lymphomas. Non-Hodgkin lymphomas being much more common. Most non-Hodgkin lymphomas are B-cell non-Hodgkin lymphomas. Although T-cell lymphomas are less common, they are getting attention particularly the peripheral type of T-cell lymphomas and the cutaneous or skin types of T-cell lymphomas, and there are several new drugs that have either been approved recently or are likely to be approved in the near future for the treatment of these 2 entities.

The B-cell lymphomas are much more common and, as we think about them, I really think of them as 3 groups of lymphomas: one being indolent lymphoma, one being aggressive lymphoma, and one being other lymphomas, which is kind of a grab bag of a number of different types, some of which are like the indolent, some of which are like the aggressive, some of which are special.

So, when we think of the indolent lymphomas, we think of follicular lymphoma being more common, we also think of marginal zone lymphomas, small lymphocytic lymphoma or SLL, and chronic lymphocytic leukemia. Even though it fits into the leukemia category and Dr. Roboz sits about 10 feet away from me, we both take care of patients with CLL, or chronic lymphocytic leukemia. Although I think we would both agree that much of how we manage chronic lymphocytic leukemia is along the lines of how we deal with some of the other indolent types of lymphomas.

And, in those diseases, in the indolent lymphomas, the usual approach is to try to control the disease for as long as possible with a good quality of life because the indolent lymphomas, in most cases, are not diseases

that we expect that our treatments, although we may hope for and I think we all are hopeful that we are making progress, and we do know that we are making progress in these diseases and people are living longer. And, in fact, many people die with these diseases, rather than from these diseases, in that they are chronic diseases, for many people, much like diabetes or high blood pressure that you don't ever get rid of, but in many cases we can manage, and patients can live relatively normally, intermittently needing therapy for their disease.

On the other hand, there are some people who, unfortunately, the disease does become more problematic and so we do need new treatments and better treatments and we all would like to, even if we do have effective treatments, we all would prefer to have less toxic and more tolerable treatment in the indolent lymphomas as well as in the aggressive lymphomas.

But the usual approach to the indolent lymphomas is that patients are typically treated with different regimens over time, often over several decades of time and often longer in some cases, with a variety of different treatments. Usually these are outpatient treatments. They usually include chemotherapy types of treatments. They often include a drug called Rituxan® (rituximab), which is a monoclonal antibody, an immune protein treatment, that helps to fight the lymphoma.

In some cases, people get treated with more intensive treatments depending on the behavior of the disease or the specific situation and, in some cases, though not most cases, patients can be treated with autologous, meaning from yourself, or allogeneic, meaning from someone else, stem cell transplants. Those are more intensive treatments, but in some cases those may be the appropriate things for patients to get even though they may have an indolent lymphoma.

So in the indolent lymphomas, much of our focus is on really new treatments that can either work better and make people live longer, new treatments that can work where other treatments have stopped working, and less toxic treatments. And so I'll just very briefly give you, before we get to the aggressive lymphomas and we'll also touch on Hodgkin lymphomas and T-cell lymphomas again, very, very briefly given the time.

But in indolent lymphomas, I'm just going to give you a sense of a couple of the new things that are coming along. Historically, indolent lymphomas have been treated with chemotherapy and there have been drugs like Leukeran® (chlorambucil) or Cytoxan® (cyclophosphamide); combinations of regimens, agents like CVP [cyclophosphamide-vincristine-prednisone] or CHOP [cyclophosphamide-doxorubicin-vincristine-prednisone]; combinations of chemotherapy. Then rituximab came along, which is an antibody-based treatment that is an immune protein that works to activate the immune system to fight the lymphoma and also can flick switches so that the cells die or are more sensitive to other treatments.

And so, over the last several years, much of the focus has been on combinations of rituximab with chemotherapy. You hear of regimens like R-CVP [rituximab-cyclophosphamide-vincristine-prednisone] or R-CHOP [rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone] combinations of chemotherapy with rituximab. There's been interest in giving rituximab by itself. It probably works a little less well than chemotherapy but is a little better tolerated than chemotherapy in most situations. So that's appealing to some people who are trying to avoid chemotherapy. And there's been a lot of attention on maintenance therapy trying to keep people in remission longer by giving them additional doses of treatment in the indolent lymphoma setting and so that's been a major focus over the past several years.

But there have been several new things that have come along. First of all, there's a drug called bendamustine that has been recently approved in the United States. It's been available. It was developed in the 1960s in Germany. It's a chemotherapy drug so it does have side effects; namely, low blood counts and nausea, but bendamustine, it's also known as Treanda®, was recently approved in the United States for both the treatment of CLL, chronic lymphocytic leukemia, and indolent lymphoma, particularly follicular lymphoma that is no longer responding to rituximab treatment. And it, in those situations, shrinks the disease anywhere from 60% to 80% of the time and it's an outpatient treatment. It can work where other chemotherapy drugs no longer work and it can work in patients where rituximab is not working, and so there are a number of studies with bendamustine or Treanda. It's something that's now FDA [Food and Drug Administration] approved, again, in those settings, but it's an agent that is also being studied as part of initial treatment. So there are studies looking at it as part of the initial treatment for indolent lymphomas in CLL or in patients that have disease that's resistant or recurrent after other therapies. It's also being used in combination.

So, for instance, there's a drug called Velcade®, or bortezomib, which is FDA approved in myeloma. You'll probably hear about that from Dr. Orlowski in a few minutes, but that agent is also active in a subtype of lymphoma called mantle cell lymphoma (MCL) and bortezomib is being combined with chemotherapy drugs including bendamustine. So, there are a variety of different clinical trials with bendamustine, with bortezomib, and that agent as well, bortezomib, has activity in various types of lymphoma, particularly mantle cell lymphoma where it's FDA approved and also follicular lymphoma.

And these 2 drugs are being combined in different studies combined with rituximab; combined with each other, combined with other chemotherapy drugs in order to try to see if they can work better and improve outcomes for patients. So, there are a variety of different clinical trials in indolent lymphoma with those 2 drugs.

Another area in indolent lymphoma or another drug that's being used both in indolent lymphoma and in other types of lymphoma is Revlimid®, or lenalidomide. Lenalidomide is a cousin of thalidomide. Thalidomide has a history, as many of you know, because of its association with birth defects, but it is a drug that was originally studied in a couple of different disorders but has become very important in the treatment of multiple myeloma, and Dr. Orlowski will mention that, but lenalidomide, or Revlimid, has activity and has been studied in indolent lymphoma like follicular lymphoma. It's also being studied in mantle cell lymphoma and in large cell or aggressive lymphoma and so you'll hear about this more from Dr. Orlowski because it's become a mainstay of therapy for multiple myeloma.

But lenalidomide, or Revlimid, is a pill. Main side effects are low blood count. It's also approved for certain types of myelodysplasia, so all 3 of us on the call have experience with it in different disease settings. And this is a drug that is in studies in a variety of different types of lymphoma and it's a pretty well tolerated drug. It does affect the blood count and it's being looked at in a variety of different studies, both alone and in combination with other drugs.

Before we leave the indolent lymphomas, I just want to mention that there are also several studies of radioimmunotherapy. Many of you have heard of Bexxar® and Zevalin®, or iodine-131 tositumomab and yttrium-90-ibritumomab tiuxetan. That's a mouthful, particularly if you're taking notes so, in particular, that's Bexxar and Zevalin. And these are agents that are being studied. They are radioactive versions of monoclonal antibodies that deliver radiation along with the antibody treatment. They can be very well

tolerated, but they do drop the blood counts unlike rituximab. These agents can work in patients where the disease is resistant to other treatments, particularly in the indolent lymphomas; they work less well in the aggressive lymphomas, but these are being studied as part of initial therapy. They're also being studied in the relapsed situation for patients who have had other therapies, particularly in combination with other agents. And so radioimmunotherapy is another useful treatment modality, particularly in the indolent lymphomas, but it's being studied in other settings.

And then, finally, I do want to mention before we leave the indolent lymphomas, the idea of vaccine treatment because many of you who have dealt with lymphoma for a while know that there have been clinical trials with vaccine treatment. The idea is to train the immune system to fight the lymphoma and most of the studies that have looked at this have generally given patients some treatment, either chemotherapy or rituximab, to try to reduce the disease, the level of disease present, and then give a vaccine made from the patients tumor to try to immunize, to strengthen the immune system to fight the lymphoma, just as you'd get a flu shot to strengthen your immune system to fight the flu vaccine.

There have been 2 of these studies that have been negative, meaning they did not show a benefit to the vaccine. There are differences in these studies. One used a chemotherapy regimen called CVP, one used rituximab; and the importance of which chemotherapy is used, how you make the vaccine, whether or not you use the rituximab as part of the treatment is a very important feature because rituximab has effects on the immune system. And the chemotherapy that you use and how well you get the disease into remission and how low it goes, so to speak, before you give the vaccine all may play a role.

So, 2 of these studies did not show a benefit to the vaccine, but some of you may have seen in the news that a third vaccine, recently in the last couple of weeks at the clinical oncology meetings, was presented and seemed to show a benefit. This was using a chemotherapy regimen without rituximab only in patients who had a complete remission, meaning the scan showed no evidence of disease after the chemotherapy, and then giving a vaccine made from the patient's individual tumor to try to keep the disease in remission longer.

And this showed that the vaccine could keep the disease in remission longer by about a year in the patients that received the vaccine. So, that's a good thing. This is an important study that showed that vaccines can potentially offer benefit, but I would say that there are some caveats to this. It was a relatively small number of patients that ultimately got the vaccine in the study, and the important thing is that rituximab can also provide a benefit, and rituximab was left out of this treatment approach. And so the question would be, well, maybe you could have had the same benefits to the patients if you had just given them rituximab, which is easier.

So, I think while we have a positive study and we're all encouraged that we did have some evidence that a vaccine can work. I think there's still much more work to be done to know who this can benefit, if it can benefit patients and before it's, in my view, ready for widespread use in all patients; but we'll see how the next several months go as these data mature, and are presented and reviewed more formally.

Next, I briefly want to move to large cell lymphoma, which is the most common of the aggressive types of lymphoma and I'm mindful that we only have a couple of minutes left in my section, but CHOP and rituximab chemotherapy is the standard treatment for large cell lymphoma. This is the most common of the aggressive

lymphomas that is a curable lymphoma in at least two-thirds of patients, perhaps a bit more. And so there are various studies looking at different chemotherapy regimens to try to improve upon CHOP and rituximab.

One is a study that is looking at a different chemotherapy regimen, a regimen called EPOCH [etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone] plus rituximab, giving one extra drug plus a little bit different way, to try to see if giving that tweak on the CHOP and rituximab regimen might be better.

The other sort of thing that many groups are doing is trying to add new drugs to the CHOP and rituximab regimen and there are a variety of different clinical trials that are looking at that to try to improve upon that.

And then there are also different studies and different classes of drugs that are being looked at in patients that relapse. Bone marrow transplant is something that's done in some patients with relapsed large cell lymphoma and there are new studies being done to try to make that better because, while it works on some people, it doesn't work in everyone. Also, there are new drugs, such as the drug Revlimid, or lenalidomide, that I mentioned earlier, that's being looked at, and a variety of other new agents. So, large cell lymphoma, the idea has generally been to try to improve upon the standard therapy with new drugs.

Before I finish, I just want to mention 2 words each on Hodgkin lymphoma and on T-cell lymphomas. First, T-cell lymphomas, there are 2 new drugs that are being looked at very carefully. One is a drug called pralatrexate. It's a newer version of a drug in the class of a drug called methotrexate that has been around a long time, and this seems to be a useful drug in certain patients with relapsed T-cell lymphoma. There is another class of drugs called the histone deacetylase [HDAC] inhibitors, and one of those drugs, romidepsin, is a drug that also seems to have activity in various T-cell lymphomas, and those drugs are in clinical trials right now that are ongoing across the country.

And then, finally, in Hodgkin lymphoma, there are a number of new approaches that are being used. One approach is to try to adjust therapy based on PET [positron emission tomography] scans to say can we treat people differently? If their PET scans look extra good, maybe we can give less therapy, or if they look less good, maybe we should give different therapy. And there are a variety of studies across the country looking at that issue.

There are also a couple of new drugs that are being looked at in Hodgkin lymphoma. One of those in particular is a drug called SGN-35. This is a special new monoclonal antibody, like rituximab, but it goes after a different target, hooked to a toxic molecule. The idea is that this is an antibody that's injected into the blood, goes around, binds to the tumor cells, and delivers this toxic drug more specifically to the tumor cell. The name of this drug is called SGN-35. This is being looked at in Hodgkin lymphoma, not the non-Hodgkin, but Hodgkin lymphoma, for the most part.

So, I would just leave the lymphoma section of the talk to tell you that regardless of what type of lymphoma one is dealing with, whether it's at diagnosis, whether it's in relapse, whether it's when nothing seems to be working, there are lots and lots of clinical trials out there. Patients should at least ask their doctor and learn either from the LLS, the National Cancer Institute, or other centers that are doing studies about what might be out there. Clinical trials, as was said earlier by Dr. Roboz, are not for everyone, but they are for more people than are currently participating in them; and so I would encourage you to at least become educated in some of these new treatments. Certainly being on this call is a good first step there, but explore these if

you're considering therapy and try to find out more information as to whether or not one of these approaches might be useful to you.

And, with that, I'll finish the lymphoma part and hand it over to Dr. Orlowski from the MD Anderson Cancer Center, who's really a superb expert in multiple myeloma for his comments.

New Strategies in Myeloma Treatment

Robert Z. Orlowski, MD, PhD

Well, thanks very much, John, for your excellent talk and for the great introduction, and I'd also like to thank *The Leukemia & Lymphoma Society*, not only for organizing this conference call, but for all of what they do for patients with hematologic malignancies in terms of support and also all of the things that they do to support research. It's one of the best advocacy organizations, I think, in the field of hematologic malignancies.

Like Dr. Roboz, I took a quick look at www.clinicaltrials.gov to see how many myeloma studies were listed, and there were 1024 entries. So, I'm going to try to be a little bit selective in reviewing what I think are some of the most promising agents. And to start with, I'm just going to review what we consider right now as our standards of care, starting with treatments available for patients with newly diagnosed multiple myeloma and, first, for those patients who may not be transplant candidates.

For those patients who need initial therapy, probably the best regimens that we have are combinations of Alkeran® (melphalan), prednisone, and Thalomid® (thalidomide); melphalan with prednisone, and Velcade® (bortezomib); or melphalan, prednisone with Revlimid® (lenalidomide); and possibly also lenalidomide with Decadron® (dexamethasone), and also bortezomib with dexamethasone. In some situations, other combinations may be appropriate, so those of you who may be undergoing therapy with other regimens, don't worry. There are many very active combinations.

Typically, because upfront therapy is now more and more effective, the efforts have currently, in the research area, been focused on trying to add agents to these combinations in order to try to improve upon both their overall response rate as well as the complete response rate, and, ultimately, that type of improvement results in benefits in terms of overall survival.

There are a couple of drugs that I think are interesting and are being added to these combinations. First of all, there are a couple of older drugs that are being looked at in combination, including drugs like Cytoxan® (cyclophosphamide), which is an oral agent that we have used for many years and also has been used IV, or intravenously, in things like non-Hodgkin lymphoma, but now also is being added to some of the upfront therapies in multiple myeloma and showing very nice benefits. Another older drug, which is being investigated again, is doxorubicin, usually in the form of a pegylated liposomal doxorubicin, which, if given intravenously, is very well tolerated and seems to add to the efficacy of both standard as well as novel agents with activity against multiple myeloma.

Two other drugs I would briefly mention that are going to be appearing in clinical trials in the near future for patients who are not transplant candidates include a drug called tanespimycin which is one example of a class of drugs that inhibit a target called heat shock protein 90 (Hsp90). This drug is also being looked at in the relapsed and refractory setting but has interesting activity upfront. As you heard from the previous speakers, patients with leukemia and lymphoma have had the benefit of having monoclonal antibodies available for therapy, which, up to now in multiple myeloma, has not been the case; but there are a few antibodies now appearing that seem quite interesting. One that I would briefly mention is an antibody known

as CNTO 328, which blocks a protein called interleukin-6, which is an important factor that is responsible for growth of myeloma and also for the drug resistance of multiple myeloma.

Moving now to patients who might be transplant candidates, probably our most active regimens in that setting would be either lenalidomide with dexamethasone or bortezomib with dexamethasone, or 3-drug combinations like bortezomib with thalidomide and dexamethasone, and bortezomib with lenalidomide and dexamethasone. Some of these have response rates that now are approaching 100% and sometimes the complete response rates from just the induction chemotherapy alone, before you ever get to transplant, can be as high as 30% to 50%. So it's going to be tough to do better than that, but, again, some of the similar themes, as I mentioned in the nontransplant patients, are being followed here where additional drugs are being added to those 2- and 3-drug regimens to try to improve upon them further. Once again, Cytoxan is being added, as is the monoclonal antibody, CNTO 328, and there are upcoming studies with a drug known as vorinostat, which is actually already approved for one type of T-cell non-Hodgkin lymphoma and seems to have activity in multiple myeloma as well.

Vorinostat is one example of a new class of drugs that are called histone deacetylase inhibitors and, basically, what these drugs do is that they change the genes that are expressed by cancer cells and make them more sensitive to some of the chemotherapies that we have. Hopefully, these trials will allow us to push the complete response rate in patients with newly diagnosed myeloma higher and higher, and eventually get up to 100%.

For those patients who undergo a transplant after their initial induction therapy, there also are a number of, I think, attractive concepts in maintenance therapy that is some kind of treatment that is given after a transplant to improve the possibility of a cure and to prolong the time until the disease relapses. [There are] a couple that I think are interesting. First of all, lenalidomide is being studied in that setting. Thalidomide has already been shown to have some benefits in some patients after transplant, and the hope is that because lenalidomide is probably generally better tolerated it will be superior to that.

You heard a little bit of information from Dr. Leonard about vaccines in non-Hodgkin lymphoma and we also here at MD Anderson have an interest in vaccine approaches after stem cell transplant, and in the next few months, hopefully by the end of the year, we will be starting a study that will use a similar approach to the one that you heard in follicular lymphoma that will take the patients' own myeloma cells, develop a specific vaccine, and then that vaccine will be administered after transplant to try to stimulate the patient's own immune system to help with eradication of whatever myeloma might be left after the transplant.

Also, in the maintenance setting, we have a study upcoming with thalidomide that is being combined with circumin. There were a couple of mail-in questions about complementary or alternative therapies being used in myeloma and other diseases, and we actually here have an interest in circumin, which is a natural product. It's actually the main component of curry, for those of you that like Indian food, and in studies in the laboratory it's been shown to have efficacy against myeloma. We're combining it with thalidomide as a maintenance therapy, both because we think the combination will be better, and also because we hope that the circumin will reduce the incidence of thalidomide-related side effects.

I did want to then move on to options for relapsed or refractory disease and we have a number of exciting options, both single agents as well as combination therapies. On the single-agent front, bortezomib, as the

proteasome inhibitor that was the first to enter the clinic, has really revolutionized myeloma therapy, but there is now a second generation of agents coming along; 2 of which are notable. One is called carfilzomib, the other one doesn't yet have a name, it's called NPI-0052, and these are both in phase I and phase II clinical trials targeting patients with myeloma. The results so far have been very encouraging, suggesting that they can be effective even in patients who have gotten bortezomib before, and I think most exciting is the fact that peripheral neuropathy, which is that numbness or tingling or burning that, unfortunately, many patients with myeloma develop, these have been very low in studies with these new proteasome inhibitors.

We spoke a little bit about lenalidomide and thalidomide, and it turns out that there's a third drug in this class of immunomodulatory agents coming that is called pomalidomide; and there have been studies presented that show that pomalidomide with low-dose dexamethasone is quite effective in patients with relapsed multiple myeloma, including some efficacy in patients who have previously received lenalidomide. So, pomalidomide is something that you should look for both in combination with dexamethasone and, hopefully, in the future in combination with other drugs.

Bendamustine [Treanda®] is a drug you heard about from Dr. Leonard but, also, bendamustine has been studied for many years in Germany and is known to have activity against multiple myeloma, and there is a registration study coming with bendamustine that, hopefully, will lead to the approval of this drug by the Food and Drug Administration for treatment of multiple myeloma. The advantage of this drug is that it seems to be effective even in patients who have had prior stem cell transplant. It's also a drug that does not cause neuropathy and is relatively convenient because the schedule that we'll be using in this trial will be IV therapy on day 1 and day 2 of every 28 days, which is fairly user friendly.

Then, finally, I mentioned some of the second-generation inhibitors of the proteasome earlier, but there also are oral proteasome inhibitors that are beginning to enter the clinic in phase I studies from a number of pharmaceutical companies and, hopefully, these will have the same benefits of drugs like bortezomib and carfilzomib, but will be easier to take because there won't be an IV infusion involved.

Then, finally, there are a number of combination regimens that are very attractive for patients with disease that has relapsed or is refractory, and the combinations often include either bortezomib or lenalidomide, or both, and add to them additional drugs; and I'll mention a few of these. First of all, there are studies with a drug called everolimus [Afinitor®], which is one example of a class of drugs that are inhibitors of the mammalian target of rapamycin, or mTOR, and the advantage of these drugs is that they cause cell death through a different pathway than many of our current drugs.

Then there's another drug called flavopiridol, which has been shown to have activity against chronic lymphocytic leukemia and other diseases, and this is an example of a class of drugs that are called cyclin-dependent kinase inhibitors; and what these drugs do is they basically stop the division of myeloma cells in their tracks and help to have other drugs like bortezomib work better.

There's a drug called perifosine that is an inhibitor of the Akt pathway. The Akt pathway helps myeloma cells to survive and avoid the effects of chemotherapy, but combining that drug which blocks that pathway, with bortezomib and lenalidomide seems to be of benefit.

We talked earlier about tanespimycin heat shock protein 90 inhibitors. They are being combined with lenalidomide and bortezomib. I mentioned vorinostat, which is the histone deacetylase inhibitor, and there is

another drug in that class called panobinostat, which is attractive as well. CNTO 328, which is the monoclonal antibody I mentioned earlier, is being combined with a number of standard agents and other monoclonal antibodies such as elotuzumab, which is directed against a surface protein on myeloma cells, called CS1, is attractive as well. The main advantage of these antibodies is that these are large molecules that are very targeted and can, in many cases, impact only on myeloma cells. Because they are too large to enter inside normal cells, the toxicity or side effects of these drugs is often much better than some of the small molecules we've talked about, which do good things if they get into a myeloma cell, but may do bad things if they get into normal cells to cause side effects.

Finally, bendamustine, again, is being combined with other drugs including bortezomib and lenalidomide, so these would all be very, I think, very attractive combinations and also single agents for you to look for if you have myeloma that has relapsed or is refractory and you are looking for novel therapies.

Finally, just as a summary, I'd like to say that the great news about multiple myeloma is that we are doing better and better for patients who have this disease, and there are a number of recent publications that suggest that the overall survival has doubled within just the past 10 years. I think the fact that we have a long list, and I've only been able to cover a few of them, of attractive new drugs that are being developed, which look like they will be likely to ultimately be FDA approved, the fact that we have so many drugs in the pipeline would suggest that we're going to continue to improve upon the survival. Hopefully, with this kind of multidisciplinary approach using small molecules, monoclonal antibodies, transplant, maintenance therapy, vaccine studies, and also alternative or complementary medications, hopefully, we'll be able to forge a regimen that will result in cure of this disease in the next 5 to 10 years.

Again, I'd like to thank you very much for your attention and for the opportunity to review some of this exciting data.

Question-and-Answer Session

Carson Jacobi, MPH

Thank you very, very much, Dr. Orlowski, and also Dr. Roboz and Dr. Leonard.

Before we get to the Question-and-Answer session, Dr. Roboz and Dr. Orlowski did talk about trial searches, and we have included in the packet that you received in the mail information about TrialCheck®. It's an online tool that can assist you in doing a clinical trial check, and you can access that by going on *The Leukemia & Lymphoma Society's* Web site. So, again, it's an online tool, but you also can always call our Information Resource Center and one of our specialists can assist you with a search.

It is now time for the interactive part of our program.

Operator

Our first question comes from Susan in Pennsylvania. Please state your question.

Susan

Yes, good afternoon. This question is for Dr. Orlowski. I'm wondering at what point you decide when to reduce the medication that your patients have. My husband has a transplant doctor and a regular oncologist. They seem to differ in what stage they want to remove or reduce some of the medications, and I was wondering if you have a good way for the patient to make a good decision, the right decision for them. One doctor works on a trend and the other doctor seems to, you know, just look at 1 set of numbers and go with that.

I'd like your opinion on that, please, and thank you for doing this.

Robert Z. Orlowski, MD, PhD

Well, thanks very much for your call, Susan. It can be difficult when you're getting different guidance from the doctors involved in a patient's care. The decision of reducing drug dosing typically is made based on 2 major factors. One is whether the patient is tolerating therapy well. If they're tolerating the therapy well, generally the trend is to continue at full doses. If they're having side effects, then the trend is generally to reduce the doses.

And the second big question is what the disease is doing, and if the disease is in complete remission, then often patients will have their drug reduced in dose with the thought of being able to keep them for a longer period on a lower dose in a maintenance-type setting. Whereas if the disease is progressing, then it may be necessary to stop that drug altogether and switch to a different one.

The other thing that may be helpful is if you're getting conflicting opinions from the 2 doctors involved, sometimes it may be helpful to get another opinion from a different expert who can look at the whole case history from a fresh viewpoint. Although, unfortunately, you may get a third opinion and then be a little bit more confused, but sometimes getting more input can be helpful, so good luck to you.

Carson Jacobi, MPH

Okay, Susan, thank you for the question. We'll take another question, please.

Operator

Our next question comes from Barbara in California. Please state your question.

Barbara

Yes, Dr. Roboz, a question. My husband is 71 with AML [acute myelogenous leukemia] and MDS [myelodysplastic syndromes]. Right now he's being treated for the MDS and he's on Dacogen® (decitabine). I'm wondering if you know of any other drug besides Dacogen that might be effective for the MDS part of his problem.

Gail J. Roboz, MD

Well, thank you very much for the question. It's always hard on calls like this because there isn't an opportunity to have a discussion but rather to just answer the question as stated. And I guess the hard part about not being able to finish out a discussion is that when you say that your husband has MDS and AML, that's actually a little bit complicated to answer.

So MDS, or myelodysplastic syndromes, is a bone marrow failure problem that sometimes evolves into AML and then the diagnosis is usually given as AML in somebody who's had MDS before. And then sometimes people are treated for AML and instead of going into a complete response or a complete remission, the marrow is left with fewer leukemic cells than when the patient started treatment but isn't in complete remission so they're called MDS. They started out with AML and now the marrow looks more dysplastic.

Dacogen, or decitabine, is FDA approved for the treatment of MDS and there are also data using decitabine, or Dacogen, for patients who are older, as a single agent for AML. So, generally speaking, it can definitely be a good choice for somebody who either has AML that has transformed from MDS or for a patient who has residual myelodysplastic features in the marrow.

In answer to your question of are there other therapies, there absolutely are. Unfortunately, for this phone call, you and I would definitely need another hour and a half together to go over those. There are absolutely other treatments that can be considered, but for right now it certainly sounds like you're in the right ballpark.

Carson Jacobi, MPH

Okay, Barbara, thank you for the question. Let's take another question, please.

Operator

The next question comes from Mary in Indiana. Please state your question.

Mary

Hi, my question is for the multiple myeloma specialist. Since my February stem cell transplant, I have developed a serious allergy to Revlimid® (lenalidomide) which I took without a problem all last fall, and can no longer take it, and I also have been recommended to not take Velcade® (bortezomib) due to neurological symptoms. I already have a spinal cord injury. What might I be able to do next?

Robert Z. Orlowski, MD, PhD

Well, thanks for your call, Mary. I'm sorry you've had those problems. Rash or allergy is not an uncommon problem that does come up with Revlimid and, in terms of the Velcade, it depends a little bit on how much neuropathy you had before, but if it was severe, then trying that drug again may not be appropriate.

The possibilities that you would have, if the disease were to relapse, would include some of the drugs I mentioned. For example, carfilzomib, which is one of the second generation proteasome inhibitors, seems to have a much lower risk of neuropathy, even in patients who have had neuropathy before from Velcade, so that would be one option. And then pomalidomide, which is a relative of Revlimid, could be an option for you as well, although because they are somewhat chemically related, there would be a risk that your allergy could also develop to pomalidomide.

But other drugs like bendamustine [Treanda®] could be used after a transplant if the disease relapsed and some of the other drugs like the panobinostat and vorinostat, or the histone deacetylase inhibitors and heat shock protein 90 inhibitors could be good candidates for you as well. So, fortunately, you've still got lots of options.

Carson Jacobi, MPH

Okay, Mary, thank you for the question. Let's take another question, please.

Operator

Our next question comes from Jeff in West Virginia. Please state your question.

Jeff

Yes, for Dr. Leonard, if he could talk about the link between Rituxan® (rituximab) and PML [progressive multifocal leukoencephalopathy].

John P. Leonard, MD

That's certainly a good question. PML is a rare neurologic disorder–I'm not going to spell it all out actually because it's easier to just say PML–but it's basically a very debilitating and, in many cases, most cases, life-threatening neurologic disorder that has been associated with, as a very, very rare complication of rituximab treatment.

PML has historically been seen in patients with disorders of the immune system, such as patients with HIV-associated disease, and of the several hundred thousand people who have received rituximab, a handful of them have had this rare neurologic side effect called PML, which is, obviously, a very severe and debilitating issue.

It is on the listing of potential side effects of rituximab and if you look at the package insert it is there. I think that it is a very, very rare complication. I mean, this is something that you're talking about one in many, many thousand people have seen this. The number of cases are in the double digits among hundreds and hundreds of thousands of people who have received it.

So, it is something to keep in mind. Like any medication, rituximab can have side effects and rarely they can be life-threatening. Certainly, again, any medication can rarely be associated with side effects. I think that for the average patient getting rituximab, PML is not something that one at all needs to worry about because statistically the chance of it occurring is very, very unlikely. But, obviously, any medication should be given, you know, based on a need for getting it and that's something that should be kept in mind, but, again, I think for most patients it is a very rare thing that most people, the vast majority of people don't have to worry about at all.

And rituximab, one of the benefits of it is that, in general, compared with many of the other treatments that we have, it is generally a very well tolerated treatment that compared to most chemotherapy drugs has not been associated with much in the way of infection.

Carson Jacobi, MPH

Okay, Jeff, thanks for the question. Let's take another question, please.

Operator

Our next question comes from Patricia in Arizona. Please state your question.

Patricia

This question is for Dr. Orlowski. My sister was diagnosed with myeloma in August 2008, and she's been on Thalomid® (thalidomide) and Decadron® (dexamethasone) and responded really well to that until about 2 months ago; and then now her numbers, her IgG numbers are coming back up a little bit. And I'm just wondering, what you would recommend given that? Is that considered refractory? And what about transplant now in that situation?

Robert Z. Orlowski, MD, PhD

Well, thanks very much for your question, Patricia. It wouldn't be, from the way you describe it, a situation where we would describe your sister as having refractory disease because it sounds like she had an initial response and then progressed. So, at least it wouldn't be primary refractory, which means no response even at the beginning although now if she's progressing on therapy, she would be considered refractory. Options would include switching to one of the other immunomodulatory drugs like Revlimid or possibly, my preference usually in these situations, is to alternate between an immunomodulatory-containing regimen and a proteasome inhibitor-containing regimen.

I think a Velcade-based combination like Velcade with the pegylated liposomal doxorubicin would be a good idea now. And if she is able to get a stem cell transplant, I think that some chemotherapy now to get her disease under better control and then moving on to stem cell transplant, would be a good plan. And, hopefully, she has access to good care. If she's there in Arizona, there are some excellent myeloma doctors available.

Carson Jacobi, MPH

Okay, thank you, Patricia, for the question and let's take another question, please.

Operator

Our next question comes from Patty in Missouri. Please state your question.

Patty

Yes, this is for Dr. Leonard. Has there been any progress in the treatment of transformed follicular lymphoma?

John P. Leonard, MD

That's an excellent question, transformed follicular lymphoma. A transformed lymphoma is basically typically categorized or it describes the idea that someone has an indolent lymphoma that changes due to changes in the genes in the tumor cells into an aggressive type of lymphoma. That is something that can happen, depending on the situation, can happen in the ballpark of over 20 years 40% of the time, and that's a very tough number to get at.

So, the bottom line is that most people with an indolent lymphoma are not going to have a transformation, but a substantial fraction of people will have a transformation of their disease into a more aggressive type over a couple of decades. And, so, that is something that needs to be kept in mind whenever the disease progresses. Has there been a transformation? Is there a change in the lymphoma?

Sometimes PET [positron emission tomography] scans can help to sort that out, meaning that the uptake tends to be higher of the injected radioisotope in a PET scan, tends to light up brighter in more aggressive lymphomas and less bright in indolent lymphomas. But, ultimately, one needs to do a biopsy to look to see if there is transformation, where it is suspected.

Typically patients with transformation of their lymphoma require more intensive therapy. So if someone's had an indolent lymphoma and received no therapy or pretty minimal therapy, the usual step is to give CHOP [cyclophosphamide-doxorubicin-vincristine-prednisone] and rituximab [CHOP-R], one of the standard therapies for the more aggressive types of lymphoma. But depending on the situation, patients with transformed lymphoma may have more aggressive disease. Sometimes that can reflect that the disease is going to be harder to treat and, in some cases, treating it more intensively with other more intensive chemotherapy regimens and/or stem cell transplantation may be in order.

Now that being said, there are many, many different types of transformed lymphoma. Sometimes people start out with an aggressive lymphoma and then it relapses and is an indolent lymphoma and, technically, that's a transformed lymphoma as well. So when you talk about the category of transformed lymphoma, there are lots of different nuances and lots of different types of people that technically fit into that categorization.

That being said, many of the new drugs that work in aggressive lymphomas can also work in transformed lymphomas. We're learning more and more about how to approach transformed lymphomas. The radioimmunotherapy drug, in particular the Bexxar® (tositumomab) agent, can be useful in transformed lymphoma for some patients, particularly those who can't tolerate more intensive treatment. And I would just generally say that most of the new drugs that are being developed and studied in lymphoma may also have utility in patients with transformed disease. And so I would say that there is progress, but because it's

something that people with indolent lymphoma need to know about and think about, but because it's such a diverse group of patients, it's a little bit hard to draw lots of big generalizations for patients with transformed lymphoma because the nuances really tell you what the best approach is there.

Carson Jacobi, MPH

Okay, Patty, thank you for the question. Let's take another question, please.

Operator

Our next question comes from Linda in Michigan. Please state your question.

Linda

Hi, thanks for all of your information. This is for Dr. Roboz. Is there any common drug regimen being suggested and used now for a relapsed CLL patient?

Gail J. Roboz, MD

That's a tough question. There are many common regimens and I would say that there isn't one that you're likely to be offered consistently if you go to different places across the country. So I would say that the good news is that there are several regimens that could be offered that would be considered somewhat standard, so you don't have to feel like you need to seek out one in particular.

I think what makes it especially hard to answer that question is in not knowing what the patient might have had before, and that's why I'm not referring to any specific drugs in my answer. What the patient has had for therapy prior to relapsing is a very important guide for what to do next. So it would be a little bit reckless to make a medication recommendation without knowing what's first.

The good news is though, in CLL, for patients who are having an early relapse, in other words not having been treated with multiple therapies yet, there are actually many options that work. The thing about CLL is that it can relapse multiple times. If a patient has CLL for many, many years, it might be coming and going a number of times. And, in general, the effort is to try to expose the disease that's coming back to something that's different from what the patient was treated with initially.

And some examples of that can include that sometimes antibodies may not have been included in an upfront regimen. They might be included in a later regimen. Sometimes there are patients who might have gotten only a few cycles of a chemotherapy-based regimen upfront. They may not have gotten, let's say Fludara® (fludarabine). We could include that down the road. Lenalidomide or Revlimid, which has come up as a number of times as one of the few drugs that actually all 3 of us can talk about as quite applicable, is also a new one that is being looked at in CLL. If a patient hadn't had it before, it might be useful to try again.

So, I think the concept should be to try, if possible, not to expose the tumor to the same stuff that it's been treated with before, with the exception that sometimes people have a really long time in between when they were last treated and when the disease comes back; and when that happens, it's quite possible that the same therapy that they got initially could actually work again and especially if the patient was comfortable with it and had an easy time with it, it might be worth a shot.

Carson Jacobi, MPH

Okay, Linda, thank you for the question. Let's take another question, please.

Operator

Our next question comes from Vivian in New York. Please state your question.

Vivian

This question is for Dr. Roboz. My question is about the drug Vidaza® (azacitidine), which is being given in combination with vorinostat for relapsed patients with AML at Mount Sinai with Dr. Silverman. I'd like to know if the drug treatment is effective if the AML patient has the chromosome defect q7 depletion.

Gail J. Roboz, MD

Okay, so the question is referring to a trial, which is combining the FDA-approved drug, azacitidine, which is marketed as Vidaza, with a histone deacetylase inhibitor. And I believe that what's being asked is whether or not a patient with a deletion 7, which is a commonly seen and unfavorable chromosomal abnormality in MDS and AML patients, whether or not there could be activity of this regimen in those patients. And there definitely can.

The exact percentages of response I don't know because I'm not even sure that those data are fully out and available, but it has definitely been shown that azacitidine alone can have responses in patients with chromosome 7 abnormalities. And I'm sure that there are already data suggesting that there are patients who have responded on the combination. I don't know what the percentages would be.

That is a challenging chromosomal abnormality to deal with because, unfortunately, patients with that do tend to have disease that wants to come back after treatment. It sounds like you, or whomever you're calling on behalf of, is on the right track with a clinical trial there and I'm sure your doctor is already thinking, hoping that this regimen is going to work well, but already thinking about alternatives should it not be successful.

Carson Jacobi, MPH

Thank you, Vivian, for the question. Let's take another question, please.

Operator

Our next question comes from Donna in Georgia. Please state your question.

Donna

Yes, this is for Dr. Leonard. I have MALT lymphoma. It started in my parotid [gland] about 3 years ago and then I was operated on for that, and about a year ago they found it in my stomach. I had *H. pylori* [*Helicobacter pylori*] also and I was treated for that. The *H. pylori* hasn't come back. I keep getting checked every 3 months. I get a endoscopy every 3 months and each one has shown tremendous regression of the MALT lymphoma. The last one was after 9 months since my antibiotics and it came back with only traces. I go again the end of July for the next one.

My question is what would be the recommended next therapy if I still have traces or even if it doesn't show at all?

John P. Leonard, MD

So MALT lymphomas, M-A-L-T, stands for mucosa-associated lymphoid tissue. That is a type of indolent lymphoma. The MALT lymphomas are a type of indolent lymphomas that tend to occur where the body comes in contact with the outside world. So they can occur in the stomach, the gastrointestinal tract, the skin, the lungs, the tissues around the eye, sometimes in the genitourinary system, sometimes in the breast. These are indolent lymphomas, generally speaking.

They have a special feature that they can sometimes be associated with particular infection. So the idea is that there's an infection that revs up the immune cells in that area, revs them up to fight the infection. Switches get broken in the immune cells in that area and a lymphoma emerges.

In particular, the most common type of MALT lymphoma associated with an infection is called gastric MALT lymphoma, meaning occurring in the stomach, and that has been associated in some people, not everyone who has this type of lymphoma but in some people, with a bacteria called *H. pylori* or *Helicobacter pylori*. And in some cases treating that infection, the *Helicobacter pylori* infection, with antibiotics can make the lymphoma regress.

Now that doesn't work in everyone. Some people have this, and this is one special type of lymphoma. So most lymphomas giving antibiotics doesn't make it go away, but in this one special type of lymphoma that sometimes happens. In this one type of lymphoma, the *Helicobacter pylori*, in the gastric MALT lymphoma, meaning of the stomach, giving antibiotics over time in some people, in many people, can make the lymphoma go away.

That process can take as long as a year or even longer. So if we're giving the antibiotics, we follow the patient for at least a year and sometimes the lymphoma can take that much of time that you have to follow by endoscopies, meaning looking down into the stomach and going from there.

Now that being said, in some people that doesn't work and there are a variety of different treatments. Whether it's oral chemotherapy, whether it's rituximab, whether it's radiation, there are a variety of different lymphoma treatments. Most of the treatments for the indolent types of lymphomas also work in the gastric MALT or other types of MALT lymphomas. If the antibiotic treatment doesn't work again, remembering, that it's that one special type of lymphoma where the antibiotics are potentially relevant.

Closing Remarks

Carson Jacobi, MPH

Okay, Donna, thank you for the question and, actually, thank you all very much for your questions. Our program has come to an end.

If you can please help me thank our panel of experts for today. We are so very grateful that they have donated their time to us today and we thank them all for the work that they do everyday in supporting families touched by cancer.

And we hope that many of your questions were answered and that the information will assist you and your families in your next steps.

Our Information Resource Center is open. The number is 1-800-955-4572 and our specialists are ready and available to speak with you to answer any more questions that you may have.

On behalf of *The Leukemia & Lymphoma Society*, Dr. Roboz, Dr. Leonard, and Dr. Orlowski, and I would like to thank you all for sharing this time with us. Good-bye and we wish you well.