

# ***Mantle Cell Lymphoma***

## ***Understanding Your Treatment Options***

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***John P. Leonard, MD***  
***June 26, 2013***

### **WELCOME AND INTRODUCTIONS**

#### ***Operator***

Greetings and welcome to the “Mantle Cell Lymphoma (MCL), Understanding Your Treatment Options” telephone and Web education program. It is now my pleasure to introduce your moderator, Mabel Maia. Thank you, Miss Maia. You may begin.

#### ***Mabel Maia***

Thank you and hello, everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you and a special thanks to Dr. Leonard for sharing his time and expertise with us today.

We have over 700 individuals participating and many international participants from Canada, China, Greece, Italy, and Iran. On behalf of The Leukemia & Lymphoma Society, thank you for joining us.

We would also like to acknowledge and thank Celgene Corporation and Millennium: The Takeda Oncology Company for their support of this program.

#### **[Slide 1 – New Developments in Mantle Cell Lymphoma]**

I am now pleased to introduce Dr. John Leonard. Dr. Leonard is the Richard T. Silver Distinguished Professor of Hematology and Medical Oncology at Weill Cornell Medical College in New York.

Dr. Leonard, we are so privileged to have you with us today, and I now turn the program over to you.

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### **PRESENTATION**

***John P. Leonard, MD***

Thank you very much, Mabel, and it's a pleasure to be here today and to speak to this audience about mantle cell lymphoma, which is a lymphoma that is a relatively uncommon type of lymphoma; but for many people can be quite challenging in trying to sort through what to expect out of it and how best to manage over the course of dealing with the disease.

#### **[Slide 2 – Lymphoma is Complicated]**

So I'm going to start with just a few background points on lymphoma itself in general and then put mantle cell lymphoma into a specific context. As this audience undoubtedly knows, lymphoma is quite complicated. There are over 60 types of lymphoma, which can be quite confusing, and over time the classifications of lymphoma keep changing. While one might think that that's a bad thing or a complicated thing, I would say it's actually a good thing because it means that we're getting more precise in figuring out how one group of patients does relative to another and how best to treat one group of patients versus another. And that is, obviously, important in making sure that you know what to expect out of the disease and how best to treat it.

But it does mean that there are lots of complicated terminology and classifications that can make it difficult to sort through. I think it is very important for people to keep in mind that making an accurate diagnosis is very important, knowing which of the many lymphoma subtypes a patient is dealing with is important and, as a patient, keeping a record of that and having the terminology—even having a pathology report yourself in your files—can be very helpful as a reference.

And that's, again, because the different types of lymphoma have different treatments. The expected goals of therapy can be quite different. In some lymphomas we have a good chance of getting rid of the disease so that someone doesn't have to deal with it again or, in many cases, not having to deal with it again. For other people, it's more of a long-term management where we do our best to control the disease and let the patient live a normal life and, hopefully, a normal lifespan despite the fact that lymphoma is there in the background and sometimes in the foreground needing treatment. It's also important to know that new ways to understand lymphoma and to treat lymphoma are changing. As a physician, I can tell you that how I treat certain types of lymphoma, including mantle cell lymphoma, is different than I did just a couple of years ago, and I have no doubt that it will be different a couple of years from now; that makes it very hard to know what to expect out of it because for an individual patient, things are changing quite rapidly.

#### **[Slide 3 – Frequency of NHL Subtypes in Adults]**

The next slide gives a bit of a pie chart on the different subtypes of lymphoma, and different lectures on lymphoma have different versions of these pie charts. The bottom line is that mantle cell lymphoma accounts for about somewhere between 5% and 10% of lymphoma patients. On this pie chart, it accounts for 6% and that's more or less the percentage of mantle cell lymphoma patients among the full population of patients with lymphoma in the United States.

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### **[Slide 4 – What features determine prognosis?]**

The first question a patient may ask is, “Well, what’s my prognosis?” Generally speaking in lymphoma, it’s complicated because it depends on a number of different factors. The first thing is which type of lymphoma one is dealing with and the age of the patient. It’s natural that older patients don’t live as long as younger patients, and that’s just, as a group. If you have a room full of 80-year-olds, they, as a group, are not going to generally live as long as a room full of 20-year-olds. The fitness of the patient [is a factor, too.] Is the patient healthy, up and around, doing things, going to work, and active? Or is the patient so sick either because of the disease or from other medical problems that they are bed bound or weak and can’t do their normal activities? In those sorts of scenarios, patients who are in less good shape and less up and around and less fit do less well.

The stage of lymphoma, meaning where did the lymphoma spread? Those are typically in cancers ranging from Stage I to Stage IV. In lymphoma, the stage is less of an important issue and most patients with lymphoma, including mantle cell lymphoma, have what we call advanced stage disease where the disease is in many places. In fact, most patients have Stage IV disease which is pretty typical in mantle cell lymphoma and not particularly out of the ordinary or exceptionally good or bad as opposed to other types of cancers where the stage of disease may be the dominant thing as far as prognosis and treatment. In lymphoma, in general and mantle cell lymphoma in particular, the stage is less important.

Having lots of areas of involvement of lymphoma outside the lymph nodes can be important in the prognosis, but, again, that also depends on the type of lymphoma we’re dealing with. Most patients with mantle cell lymphoma have evidence of the mantle cell lymphoma outside the lymph nodes in various places. The blood test can be important as well as other special tests depending on the specific type of lymphoma. So, lots of different things figure into it. It’s not just one feature that determines for a physician or patient what’s the prognosis, what’s the treatment.

### **[Slide 5 – B-cell non-Hodgkin Lymphoma]**

So, in general, among different types of lymphoma, we have indolent lymphomas that are generally not curable, but for many people can be chronic diseases that we can control over many years, and while they can be serious for some people, for others they are things that people can live with rather than die from, a chronically managed sort of thing. We have aggressive lymphomas that can be curable for many people though not all with combinations of chemotherapy and an antibody or an immune protein treatment called rituximab (Rituxan®). Then we have mantle cell lymphoma, which is somewhere in the middle, which is something that for most patients is something that we can control over years, but is something that is likely to be up and down, something that a patient has to deal with on and off over the course of several years, and, in many cases, a natural lifespan depending on the overall situation.

### **[Slide 6 – Mantle Cell Lymphoma (MCL)]**

Mantle cell lymphoma, again, accounts for about 5% to 10% of patients with lymphoma. It is predominantly something we see in male patients, and it’s really unclear as to why that’s the case. The average patient with mantle cell lymphoma is in their mid-60s and, again, is more commonly a male. There are a variety of different treatment options and the clinical course, or how the disease plays out, can be quite variable depending on many, many different factors. It also is not always

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predictable so that we can't always look at a patient and say, "Well, you're likely to do better, you're likely to do worse," although there are a few things that give us some hints in that regard.

Interestingly, mantle cell lymphoma is characterized by a specific genetic change, what's called the 11;14 translocation. That means in the tumor cells chromosome 11 and chromosome 14 are broken and hooked up to each other abnormally, and that results in that turning on genes that makes cells proliferate (the mantle cells)—meaning making them grow. So, this genetic change that turns on the cycling of the cells that causes the cell to grow and to divide is something that's characteristic in mantle cell lymphoma. In fact, looking for this 11;14 abnormality through very sophisticated molecular tests often helps us make the diagnosis because we expect to see those genetic changes in patients with mantle cell lymphoma, so that confirms the diagnosis.

### **[Slide 7 – MCL Initial Treatment Options]**

One of the more challenging things about mantle cell lymphoma is how exactly do you treat it? There are a variety of different treatment options. Typically speaking, we approach patients either in a less intensive fashion or a more intensive fashion. I can tell you that there is a lot of debate in the community of physicians who treat mantle cell patients as to which approach, a more intensive, meaning stronger treatment, or a less intensive, meaning easier treatment approach, is best. At medical meetings we often have debates and discussions where we discuss the pros and cons of treating this more aggressively or less aggressively. Some physicians are very passionate about this and feel very strongly that if you're a younger patient who's in good shape, we should give you the stronger treatments because you're in position to tolerate them. Others say, "Well, you know, these more intensive treatments, while they may keep the disease in remission for a long time, they have side effects, they have toxicities, and it's not entirely clear that throwing the kitchen sink at mantle cell lymphoma makes people live longer in the long term."

And so, there's a lot of debate about this, and I think it's very appropriate to say that there are lots of ways to approach mantle cell lymphoma and very little evidence that one way is necessarily proven to be better than the others. At many centers, these decisions are based on what kind of shape the patient is in. If the patient is elderly, if his/she has lots of medical problems or is more frail, the decision may be to use a less intensive treatment option, which typically is chemotherapy. There's a regimen called R-CHOP (rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone), there's a regimen called R-bendamustine (R-Treanda®). We'll come back to those in a second.

These are typically outpatient treatments that are combinations of chemotherapy with a drug called rituximab, which is an antibody treatment. These are outpatient treatments that do have some side effects in some cases: low blood counts, infections, sometimes hair loss, and sometimes some nausea. But these are generally treatments that people feel 70% to 80% of their normal self. They generally treat the lymphoma; it generally works for a couple of years, and then at some point down the line the lymphoma comes back. Now, this doesn't mean the patient dies at that point, it doesn't mean that they're sick at that point, but these do not generally eliminate the lymphoma indefinitely for years and years and years.

On the other hand, many centers say that well, if you're a younger patient who's in good shape, we should treat you very intensively—very intensively means giving you stronger treatment because you

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can tolerate that treatment and because that treatment may keep you in remission for a longer period of time even though we don't generally expect it to cure the lymphoma so it never comes back. Even if the evidence that you live longer with these stronger treatments, even though you stay in remission, can be somewhat debatable in the minds of some people. The stronger treatments tend to either follow up one of the chemotherapy regimens like R-CHOP with something called a stem cell transplant, a more intensive way of giving chemotherapy—we'll come back to that in a minute—or with the regimens of chemotherapy that are stronger, given in the hospital. A regimen called hyper-CVAD (cyclophosphamide-vincristine-doxorubicin-dexamethasone), which is a more complicated regimen that, again, has more side effects, often requires hospitalization as part of the treatment, and generally keeps people in remission longer but doesn't necessarily make people live longer. For many people, the side effects are manageable and it's worth going through a very strong treatment if you're going to go for several years without having the disease come back.

On the flip side, others can't tolerate the treatment or don't want to tolerate the treatment. In the absence of knowing that it's going to get rid of the disease or make one live longer, then it is of less clear benefit. And so, these are the issues that are debatable. Different doctors, different patients have varied opinions about this, and we'll come back to some of this in a minute.

### **[Slide 8 – If on “watch and wait” when to start treatment?]**

On the flip side, there is some evidence, and our group at Cornell has been one of the groups that have led this concept, that you could “watch and wait” with mantle cell lymphoma. “Watch and wait”, meaning observing the patient without treatment, is something that we do in other indolent lymphomas. In fact, it turns out that in some patients with mantle cell lymphoma you can watch the patient without treatment because if the lymphoma is just sitting there, it's not causing any problems, if the patient has no symptoms and early treatment isn't going to necessarily get rid of the lymphoma, you could argue well let's wait and treat it at some point in the future because there's no real need to rush to go and treat it if early treatment is not going to make you do better in the long term. And so for some people, and in some series that can be as few as 10%, 20%, perhaps a little bit more, if the lymphoma is just found but the patient has minimal symptoms, one can watch it and delay treatment for a while.

Indications or reasons to do treatment could be large lymph nodes, many sites of the lymphoma, a rapid change over time, symptoms or laboratory problems that would say, “We better get started on treating this because it's either causing trouble or going to cause trouble sometime soon.” So, those are the reasons if a patient is being watched at the beginning or watched if their disease relapses, those would be the reasons to start to think about doing something.

### **[Slide 9 – Rituximab Chimeric Anti-CD20 Monoclonal Antibody]**

Rituximab is an antibody treatment. Antibodies are immune proteins that bind to the lymphoma cells, activate the immune system to fight lymphoma, and also flick switches on the lymphoma that make them more sensitive to treatment. Rituximab, this antibody treatment, this immune protein, is typically used in B-cell lymphomas and most lymphomas, including mantle cell lymphoma. Rituximab binds to something called CD20, which is a marker on the surface of the lymphoma cells. This slide has a fair amount of information on rituximab. The bottom line is that when we give chemotherapy to patients with mantle cell lymphoma and other lymphomas, we give rituximab along with it and it generally

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makes the chemotherapy work better. In some situations, we give maintenance rituximab, additional doses of the rituximab, to try to keep the lymphoma in remission. And we'll come back to that in just a few minutes.

Rituximab is typically given along with chemotherapy in mantle cell lymphoma, and it is sometimes given as a maintenance treatment after chemotherapy in mantle cell lymphoma. The main side effects of rituximab include fever, chills, shakes, and a reaction to it. There can sometimes be some low blood counts from it and sometimes there can be some infections from it. But, in general, it's a pretty well tolerated drug for most patients.

### **[Slide 10 – Randomized Phase III Study of First-Line B-R versus CHOP-R in Indolent NHL]**

Historically for older patients with mantle cell lymphoma and some younger patients with mantle cell lymphoma, we used a regimen called R-CHOP, a combination of chemotherapy drugs given every three weeks along with rituximab, the antibody treatment that we talked about. CHOP-R in mantle cell lymphoma, generally keeps the disease quiet for somewhere on the order of about two years—sometimes shorter, sometimes longer. The R-CHOP makes your blood counts go low, can predispose you to infection, cause you to have hair loss, and you can have some other side effects with it.

### **[Slide 11 – Bendamustine + Rituximab vs CHOP + Rituximab]**

There is a new drug called bendamustine, which is a chemotherapy drug also given as an outpatient, also in combination with rituximab. We've had a couple of what we call randomized trials across a variety of different lymphoma types for patients, that compared bendamustine-rituximab (B-R) to R-CHOP. The bottom line of these studies is that the bendamustine-rituximab seems to be a very appropriate treatment for many patients with mantle cell lymphoma. The B-R regimen does not generally cause hair loss, has a little more in the way of side effects, but has fewer infections. About 90% of patients with mantle cell lymphoma have disease shrinkage. In about half of people, the disease goes into remission where you can't see it there; it doesn't mean it's cured, but at least the scans look much improved. In general, durations, meaning how long it lasts, is somewhere in the range of two to three years.

### **[Slide 12 – Issues in Treatment of MCL in Older or Less Fit Patients]**

For many people, particularly older people, we have switched to the bendamustine-rituximab regimen instead of the R-CHOP regimen in mantle cell lymphoma because the side-effect profile appears to be perhaps better and the efficacy, as far as controlling the lymphoma, seems to be at least in the same ballpark as the R-CHOP regimen. And so, bendamustine-rituximab is being used much more commonly.

In older patients with mantle cell lymphoma, we have several issues. One is, do we “watch and wait” in an individual patient? If you're asymptomatic, feeling well, let's leave it alone for a while. Do we use bendamustine-rituximab? I showed you that this is becoming more commonly used. Do we use maintenance rituximab? After the chemotherapy, do we keep patients on maintenance rituximab one dose every two to three months for a period of time to try to keep the disease in remission longer?

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There is one study after R-CHOP suggesting a clear benefit of the maintenance rituximab in mantle cell lymphoma. We don't know yet in the bendamustine-rituximab, but many people have extrapolated to that scenario and are also giving maintenance rituximab after bendamustine-rituximab in mantle cell lymphoma. That's not based on the studies with the B-R regimen. It's based on extrapolating from the studies with R-CHOP, so there are still some things to learn there.

Now, the other issues that come up are, can we get rid of chemotherapy? If chemotherapy has side effects and it doesn't get rid of the disease, are there other options that we can use? Certainly in clinical trials, we are looking at regimens that avoid chemotherapy to potentially control the disease in a different way, and obviously clinical trials, like in any type of lymphoma, are quite important.

### **[Slide 13 – Issues in Treatment of MCL in Younger or More Fit Patients]**

Now for younger patients with mantle cell lymphoma, we have a variety of other questions that in some ways are similar, in some ways are different. One is, again, in a younger patient who's feeling well, can we "watch and wait" and delay therapy? I personally believe that is a reasonable option for certain patients. Are more intensive treatments better? If we give stronger treatments, if we give stem cell transplants, are patients more likely to live longer? It's unclear. They are more likely to have side effects, but they are also more likely to stay in remission, meaning go a longer period of time before they have to deal with the disease again. And so the tradeoffs of more versus less intensive treatment are less clear. We also are moving toward chemotherapy-free regimens in younger patients, although some doctors think that we should stick with the chemotherapy in that situation. The clinical trial options also very important for this group.

### **[Slide 14 – Stem Cell Transplantation]**

So, one thing that's important to keep in mind in mantle cell lymphoma is the concept of stem cell transplantation because many patients, particularly younger, fitter patients, are treated with stem cell transplantation. There are two ways of doing stem cell transplantation. One is called autologous, meaning from yourself, which is basically a fancy way of collecting your own blood stem cells, putting them in the freezer, giving high doses of chemotherapy, enough to keep the disease in remission longer, but also to wipe out or knock out the normal blood counts, but then rescuing the patient with their own blood stem cells that were in the freezer collected before the high doses of chemotherapy to help rescue the blood count. So that's autologous stem cell transplant.

The allogeneic stem cell transplant, which is from another person, is one that is more complicated. You have to have a match. It also has more side effects, but it can be more effective against the lymphoma cells and so there's a tradeoff there. When we talk about stem cell transplant, for most patients, we're talking about autologous or from yourself, but in some scenarios allogeneic transplants, or from someone else, are also to be considered. These are very complicated issues and one that if a patient with mantle cell lymphoma sees a stem cell transplant doctor, the suitability for one type versus the other depends on many different variables.

### **[Slide 15 – 2 Opposite MCL Management Approaches]**

So, in general, there are two opposite approaches I would say to mantle cell lymphoma. One is to be very aggressive with the treatment, to put up with the side effects, to have a longer period of remission, to hope that you will live longer. These may include a stem cell transplant. It may include a

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stronger treatment like hyper-CVAD with the hope that this stronger treatment will pay off in the long term, but the downside is more in the way of side effects.

Then there are gentler strategies saying, “Hey, if we’re not going to get rid of the disease no matter what we do because it’s something that tends to stay with us, but we can control it, why use an aggressive treatment? Why not use a gentler treatment with fewer side effects with the idea that the quality of life will be better using a less strong treatment?” On the other hand, one might argue will your quality of life be better if you go a long time after a more toxic treatment without having the disease to deal with for several years? And the question of the gentler strategies are relating to the idea of whether this could be less effective in the long term.

And so, different doctors have different styles. I have to say that our group at Cornell tends to be more focused on the less intensive treatment, but that doesn’t necessarily mean it’s correct and that doesn’t necessarily mean that other very good centers don’t take a more aggressive approach, particularly in younger patients who can tolerate more intensive treatment. This is something that we debate regularly among mavens in lymphoma who are dealing with the issues and trying to improve our treatments.

### **[Slide 16 – Biological Effects of Bortezomib (Velcade®)]**

Next I want to focus on a couple of different drugs that are relevant to patients with mantle cell lymphoma. One is bortezomib (Velcade®). This is an U.S. Food and Drug Administration (FDA)-approved drug for patients with mantle cell lymphoma with relapsed disease. This is what’s called a proteasome inhibitor. Proteasomes are what I would liken to be the garbage can of the cell. So, if you keep the lid on the garbage can, the garbage accumulates in the cell, the cell gets unhappy, the cell gets stressed. It’s more likely to die, it’s more likely to get effectively treated by chemotherapy and other treatments. So inhibiting the proteasome, or the garbage can for the cell, is what bortezomib does. It can be useful in various forms of cancer including mantle cell lymphoma.

### **[Slide 17 – Bortezomib (Velcade®) in NHL]**

Bortezomib is an FDA-approved drug for mantle cell with patients whose disease has relapsed. It’s given either intravenously or subcutaneously. It’s a quick injection either under the skin or in the vein. It’s given two days a week for two weeks in a row out of three. The main side effects are neuropathy, numbness and tingling of the fingers and toes, fatigue, and low blood counts, particularly platelets. It shrinks the disease as a single agent, meaning by itself, in about a third of patients with mantle cell lymphoma usually lasting about 6 to 12 months. For some patients, it works for a longer period of time. It’s being used in various forms of lymphoma either alone or in combination with other things. So, bortezomib is something that many patients with mantle cell lymphoma receive, particularly when their diseases returned after prior treatment.

### **[Slide 18 – Lenalidomide (Revlimid®) in NHL]**

Another drug that was recently approved in mantle cell lymphoma was lenalidomide (Revlimid®). This is a drug that’s approved for multiple myeloma, as is interestingly bortezomib, as well as myelodysplasia, a bone marrow disorder, and mantle cell lymphoma. Lenalidomide is a cousin of thalidomide (Thalomid®). It’s a pill that has a number of different effects, including affecting the immune system, directly killing tumor cells, and interfering with blood vessel formation in the tumor.



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As a pill given three weeks on, one week off, it's main side effects are low blood counts, rash, and fatigue. It shrinks the disease in most lymphoma subtypes to a degree. In patients with mantle cell lymphoma who have had previous treatment, including previous bortezomib, it shrinks the disease in about 25% to 30% of patients usually on the order of about a year or just over a year. So, it's something that by itself can work in mantle cell lymphoma patients who have had prior treatments and, in fact, is also being studied in other lymphomas and in combinations with standard treatment.

### **[Slide 19 – Key New Drugs in MCL in Clinical Trials]**

There are a number of new drugs in clinical trials that patients with mantle cell lymphoma should know about, and I would strongly urge patients with mantle cell lymphoma to learn about clinical trials and think about clinical trials. These are new drugs that are being studied in mantle cell lymphoma and have very interesting early results. Ibrutinib (PCI-32765), which is an inhibitor of something called BTK or Bruton's tyrosine kinase, is a pill that is active. It basically flicks switches in an important pathway in mantle cell lymphoma called Bruton's tyrosine kinase and that pathway is turned on. The turning on of the pathway helps keep the cells alive. It's like a switch. It helps keep the cells alive and helps them to stay alive and be resistant to treatment. By flicking the switch back, the cells can be unhappy and, in fact, it turns out in clinical trials, this is a very effective and well tolerated drug in patients with mantle cell lymphoma. Now, I say "effective." That's probably not the best term. I would say about 70% of patients have some improvement in mantle cell lymphoma with ibrutinib in the early clinical trials. There are a number of different ongoing studies because there's a lot of interest in the community about ibrutinib.

Another drug is idelalisib (CAL-101). It hits a different switch. It's also a pill. This switch is called PI (phosphoinositide)3 kinase and this drug also shrinks the disease in mantle cell lymphoma. In the early studies about 40% to 50% of the time but it tends not to work for a very long time and so there are other studies going on that are combining it with other treatments, including in mantle cell lymphoma.

A third drug is called palbociclib (PD-0332991). This is a drug that inhibits the cell cycle, the pathway that the cells go through to divide. This has been studied in mantle cell lymphoma. Our group at Cornell and others have been looking at it and it seems to be promising.

And then there's a drug called ABT-199 (GDC-0199), which is a drug that inhibits apoptosis. Apoptosis is the process by which cells normally die and this is a drug that essentially interferes with pathways that are keeping the cells alive and helping the cells to die more normally. There have been a very small number of mantle cell lymphoma patients treated with this drug with good results. It needs to be studied much more broadly.

In the last minute or so before I open this up to questions, I just want to make a few final comments. This relates to, "So what is a patient to do?" I would assume that the audience is comprised of patients who are newly diagnosed (haven't had treatment), patients who have relapsed mantle cell lymphoma, and patients who have mantle cell where the disease has come back several times and the patient may be worried about their options.

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### **[Slide 20 – So what is a newly diagnosed patient to do...?]**

So, if you're newly diagnosed, you want to be clear of your diagnosis, you want to get educated—and this is a good first step—about lymphoma, mantle cell lymphoma, and about clinical trials. You need to develop a strong care team of physicians, nurses, nurse practitioners, other support, people that are experts in lymphoma, particularly mantle cell lymphoma which is not the most common disease. You want to make sure that this group is familiar with mantle cell lymphoma, has access to clinical trials, and, obviously, you need the support of your family and friends. You want to establish the expectations of your treatment. Do you need treatment right now? What is the goal of your treatment? Are you expecting to have a long remission? Are you trying to manage the disease with as few side effects as possible? You can make your plans, but you need to be prepared that the disease may change or may surprise you. And then, again, you need to try to live your life as best you can and not let the disease, when you can live a normal life, really try to live your life and enjoy it and try to put the lymphoma into the background as much as you can.

### **[Slide 21 – So what is a patient in remission to do...?]**

If you're in remission, it's a little bit harder because the disease at some point is expected to come back, so you need to think about what you can do to avoid that but don't go crazy about that happening. Remain educated about what's going on in lymphoma so that you're prepared if the disease comes back so you know what to do think about to do at that time. And try to enjoy being in remission but also do what you can to support lymphoma research and progress in lymphoma, which is very, very important for all of us.

### **[Slide 22 – So what is a patient who has relapsed to do...?]**

And if you're a patient who's had disease that's relapsed, you want to be sure it's really a relapse. You need to be sure you need treatment at this point in time, understand the implications: what do you need to do about it, what is the big picture, review the different treatment options, consider clinical trials, and remember that it is usually not the end of the world because we have lots of different options in our armamentarium to treat mantle cell lymphoma and other patients.

### **[Slide 23 – The good news...]**

So the good news is that, basically, we have lots of different options in lymphoma, including mantle cell. Things are changing. In my mind, the new drugs are definitely improving how patients are doing. We're learning more about the disease, the biology, and there are lots and lots of people along with you working in this area trying to improve outcomes for mantle cell lymphoma.

### **[Slide 24 – Still room for improvement...]**

But we still need to make progress, we still need to work together, patients really do need to participate in clinical trials because that's how we make all of the progress that I'm telling you about today is through participation in clinical trial. Unfortunately, through government cuts and other economic issues, there is decreasing research funding; and so if you're in a position to support research activities, like through the LLS and other organizations, I would encourage you to do so because this is essential to our progress.

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### **[Slide 25 – Conclusions]**

But do be encouraged about the progress. There's a lot happening. Patients are doing better. And, certainly, at any time you're thinking about a new therapy, consider participating in clinical trials because that really is the way forward into the future.

So, with that I will stop, and thank you very much for your attention, and I look forward to discussing any questions.

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### **QUESTION AND ANSWER SESSION**

***Mabel Maia***

#### **[Slide 26 – Question and Answer Session]**

Thank you so much, Dr. Leonard, for such a clear and informative presentation. This is very helpful to our audience.

It is now time for the Question and Answer portion of our program. For everyone's benefit, please keep your questions general, without many personal details, so Dr. Leonard can provide an answer general in nature.

Dr. Leonard, our first question comes from the Web. "I was first diagnosed with CLL (chronic lymphocytic leukemia) and now after the FISH (fluorescence in situ hybridization) test I've been told I have mantle cell. My blood counts have been more or less the same for the last two years and I only have two nodes a little bit bigger than usual. Does that mean my kind of mantle cell is indolent? Is there any benefit in doing treatment right away?"

***John P. Leonard, MD***

This question highlights a couple of important issues. One is knowing your exact diagnosis and sometimes mantle cell lymphoma can be difficult to sort out. It can look like and present itself like other types of lymphoma. One of those types is called CLL, chronic lymphocytic leukemia, which is actually more like a lymphoma. It typically has a high white blood cell count and swollen lymph nodes and an enlarged spleen, which is a fancy lymph node in the abdomen.

The FISH test is a special test that looks for that broken chromosome 11 and chromosome 14, which is very helpful. It sounds like this patient had a presentation to the doctor that seemed like CLL but when this FISH test was done saw that genetic change which was the 11;14 change that goes with mantle cell lymphoma. So, again, it reiterates knowing your diagnosis and making sure the right tests are being done to sort that through.

Now, with that being said, this person describes a course that the disease has been relatively quiet. There is a subgroup of patients with mantle cell lymphoma, usually about 20% of people but it really depends and can be hard to know, where if the disease had been slowly growing, is not causing any problems, you don't have to necessarily rush to treat it. And, in fact, we don't have a lot of evidence that people actually live longer and do better, so there's really not a great reason to start treatment because there's no clear benefit to doing it in the long term. And so this person it looks like has the benefit of hindsight. The disease has been puttering along for two years. So, in general, that would be a good background of information that the disease is growing slowly and that continuing to watch it rather than intervening and doing any treatment might be quite a reasonable thing to do.

There are other people out there that present with a variation of this theme. If the disease is being quiet and you know it's being quiet, then certainly watching it for a while is a reasonable thing to do. In fact, the best way to predict if that's going to happen is to just take a few months and watch it and

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see what happens over the course of a few months and see if it's puttering along versus if it's growing, then that would be a good reason to go ahead and make an intervention.

***Mabel Maia***

Great, thank you for that question. Operator, we'll take one from the telephone audience, please.

***Operator***

Thank you. Our next question comes from Cathy calling from Michigan. Please state your question.

***Cathy***

Yes, thank you, doctor. I was wondering what are the possibilities/probabilities that an angioimmunoblastic T-cell lymphoma (AITL) could turn into a mantle cell lymphoma?

***John P. Leonard, MD***

An angioimmunoblastic T-cell lymphoma is a very different type of lymphoma. T-cell lymphomas are unlike B-cell lymphomas. B-cell lymphomas are about 90% of lymphomas. T-cell lymphomas are about 10% and there are many different subgroups of T-cell lymphomas. B-cells are kind of like the army cells of the immune system. T-cells are much less common; they're perhaps the marines of the immune system, a smaller group that does a little bit different job. So, because these are different – mantle cell is a B-cell lymphoma, angioimmunoblastic is a T-cell lymphoma – it would not be expected that one could go to the other.

In that sort of scenario, I would want to be very clear on the diagnosis. It may be that one of the diagnoses is incorrect. It may be that the person has actually two lymphomas in one, which occasionally can happen. It would be unusual, but occasionally could happen and that would be very important in sorting through. When one chooses a treatment, you want to, obviously, be very clear on what you are treating and making sure that the treatment was directed toward the right type of lymphoma.

***Mabel Maia***

Thank you so much for calling in with that question. Dr. Leonard, our next question comes from the Web. "Can surgery cause a lapse of the immune system allowing the mantle cell lymphoma to become aggressive versus indolent?"

***John P. Leonard, MD***

So what triggers a change in the biology or the pattern of lymphoma is one that's of great interest, right? If we could understand why this lymphoma was acting indolent or why this lymphoma was acting aggressive or what factors made it change from one type to the other, that would be very helpful because we would either do or not do the things that resulted in a more favorable course.

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Unfortunately, there's little evidence of that and there is as far as things that we can intervene with in order to influence a patient's outcome.

Surgery is something that occasionally needs to be done for patients with lymphoma as well as other people who don't have lymphoma, obviously, have reasons for surgery. There's no indication that surgery or such a procedure would alter the change in lymphoma's activity or in the course of lymphoma. So, I would say that I would not expect that surgery would make a lymphoma become more aggressive or cause more problems for a patient.

***Mabel Maia***

Thank you for that question. Operator, we'll take the next one from the telephone audience, please.

***Operator***

Our next question comes from Mitchell calling from New York. Please state your question.

***Mitchell***

Is there any evidence of chronic use of NSAIDs (nonsteroidal anti-inflammatory drugs) being linked to the findings of mantle cell lymphoma or the translocation 11;14 position?

***John P. Leonard, MD***

Thanks for your question. NSAIDs are nonsteroidal anti-inflammatory drugs, drugs along the lines of aspirin or ibuprofen, things that could be taken for a variety of different medical conditions. These are anti-inflammatory drugs.

There are interesting links between inflammation and cancer and there have been a number of different attempts in various cancers to try to use anti-inflammatory drugs to cut inflammation and, obviously, then either lower the chance of getting a cancer or improve the outcomes for patients with cancer.

In lymphoma, to my knowledge, there aren't any good data that link nonsteroidal anti-inflammatory use to either getting a lymphoma or the outcome of a patient with lymphoma. So to my knowledge, there's no evidence that that can influence how lymphoma patients do.

***Mabel Maia***

Thank you for that question. Our next one is from the Web. "I had a stem cell transplantation in 2010. I am now in remission as of a PET (positron emission tomography) scan in April 2013. How often and for how long should I continue to have PET scans? I still have a lot of fatigue and very little balance. Will this ever go away?"

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***John P. Leonard, MD***

So the emailer asks a very important, or the emailer I should say, ask a very important question, and that's relates to how often one does scans for patients with lymphoma and for mantle cell lymphoma in particular. And that's gotten a lot of attention at the American Society of Clinical Oncology (ASCO) meeting, which was earlier this month [June 2013]. There were a couple of presentations focused more on large cell lymphoma (LCL) and Hodgkin lymphoma suggesting that there was very little value to doing follow-up scans to patients in remission. Whether or not one can extrapolate that to mantle cell lymphoma and other subtypes remains to be seen.

So the concept of not doing so many scans is basically the observation that most of the time when the disease has come back and if it's come back to a point that it needs some treatment, that it's not that hard to find and that you don't need a scan to find it. Most of the time if the disease is back and there needs to be some treatment for it, the bottom line is that usually the patient has a symptom, the patient feels a lump, the laboratory studies on the patient show something, or the doctor feels something that then directs an evaluation and reveals that the disease is back.

Typically speaking, if the patient feels fine, the physical examination is fine, the laboratories are fine, and there's nothing going on during a routine office visit or from the patient's perspective, the idea that you're going to find something on a scan is very unlikely. And so, that's an argument for all types of lymphoma, I would say, that doing lots of scans if you're in remission, feeling well, doing well, your labs are fine and your doctor doesn't find anything, you probably don't need to do a lot of scanning.

Now, with that being said, these sorts of decisions are individualized and it's hard to generalize should you do scans or how often should you do scans. But, in general, I think one should ask oneself. One shouldn't automatically do scans at regular time intervals. One should ask oneself, "Is it likely to find something on this scan based on the whole picture that we're going to need to find out about because we need to do something about it?" And if you're feeling well and there's nothing going on from the perspective of the patient and the doctor, there's probably not going to be much on a scan, whether it's mantle cell lymphoma or other types of lymphoma.

From the standpoint of dealing with side effects of a stem cell transplantation and intensive chemotherapy, it's very hard to generalize. These treatments do have some side effects. Some of these treatments such as fatigue and other issues that the person mentions, are things that can improve over time but it may take months. In some cases, it may take years. And sometimes it may not resolve at all. It just may be something that one has to deal with chronically. So, I would urge you, not knowing the details of your symptoms and your situation, to follow-up with your doctor. In some cases, things can continue to improve as far as side effects but sometimes they can be more long lasting.

***Mabel Maia***

Thank you for submitting that question. Operator, we'll take the next one from the telephone audience, please.

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### ***Operator***

Our next question comes from Paulette calling from California. Please state your question.

### ***Paulette***

Good morning, doctor. Could I ask a question? Let me ask you, why is it that mantle cell is not curable when a lot of the other lymphomas like the large cell lymphomas are? I know that's kind of a strange question, but I'm just curious.

### ***John P. Leonard, MD***

So that's a great question and, as you allude to, there are many types of lymphoma, some of which can be lymphomas that the treatment is able to get rid of the lymphoma and it may not come back, although that may be something that is only in a group in some patients with that type of lymphoma like large cell lymphoma but not all. Other types of lymphoma, despite even very strong treatments, we typically expect them to come back eventually, and mantle cell is one of those, and so I don't have a good answer. If I knew exactly why it was that mantle cell came back, I would do my best to design a treatment that could go after that switch or that problem. I can tell you that we are working very hard to do that, but we don't have the answer.

Now, with that being said, I am very optimistic with some of our treatments that either, for many people, we will ultimately get to a point through new combinations and understanding things and new drugs that we can cure mantle cell lymphoma or we can at least turn it into something chronic that people can live a normal life with and a normal lifespan and die with it rather than from it, and so that would be pretty good. Certainly not as good as getting rid of it altogether, but certainly a major advance.

I think we are making progress and these are challenging things to sort through and that's why we're doing the research to try to see what we can do to move things forward in that regard.

### ***Mabel Maia***

Thank you, Paulette, for calling in with your question. Our next one is from the Web. "Are treatment options different for patients with the blastic variant (BV) of mantle cell lymphoma?"

### ***John P. Leonard, MD***

So the blastic variant of mantle cell lymphoma occurs when a lymphoma changes to be more aggressive. The cells can evolve and become more aggressive, grow more quickly, and can be more resistant to treatment, and so this is something that is hard to know exactly how often it happens in mantle cell lymphoma patients. It may be as low as 10% or 20% of people where this happens. It may be higher than that. Sometimes it's a diagnosis where the disease is more aggressive. Sometimes it's something that evolves over time.



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In general, with blastic mantle cell lymphoma, when the disease has taken this aggressive turn, we typically, if we're treating it with chemotherapy, we tend to use stronger chemotherapy, more intensive chemotherapy. However, we're still learning with the new drugs, including ibrutinib, including lenalidomide, including bortezomib, exactly how well these new drugs work in the blastoid type. So, that's a very important area of research. But, in general, when a lymphoma, a mantle cell lymphoma has become the blastoid type, it means it's going to be harder to treat and, typically, we have to treat it more aggressively or we have to think about one of the new drugs that might have the potential to help in that situation.

***Mabel Maia***

Thank you for submitting that question. Operator, we'll take the next one from the telephone audience, please.

***Operator***

Our next question comes from Jennifer calling from Tennessee. Please state your question.

***Jennifer***

Yes. My mom is on the IPI-145 and, Dr. Leonard, it's been a pleasure to hear you again today. We saw you a year ago in New York, and we wanted to know the durability, if there are any statistics out, of this trial drug.

***John P. Leonard, MD***

So the IPI-145 drug is another drug in clinical trials. It is a drug. It wasn't on my slides because it's a little bit newer. It is also an inhibitor of the pathway or the switch called PI3 kinase. I mentioned one drug called idelalisib. There is another drug, the IPI-145, which is, again, a newer drug. It's another inhibitor of PI3 kinase. So, these are different in that they are made by different companies, but they also flick a little bit different switches and types of this PI3 kinase pathway. This is a drug that's earlier in clinical trials. It's being studied in a variety of different lymphoma subtypes. There are several mantle cell lymphoma patients who have received this drug as well as other types of lymphoma patients who have received this drug, and I think it's very early.

It's encouraging that this drug seems to have activity in mantle cell lymphoma as well as other places, but it's something that's very, very early. You have to know that for a patient on a trial it's great to be seeing results, but then the question is, as the caller asks, "How long is it going to last?" The fact of the matter is if it's only a handful of people who've gotten the drug and only a few of them have this particular type of lymphoma, it would take hundreds of people and years of follow-up to know how long we can expect it to last. It's really too soon to say. Any number that anyone told you it would be, "Well, we had a couple patients here and a couple patients there." They wouldn't really be good numbers that you could hang your hat on.

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I'm glad that things are going well and it can be challenging to decide what do we expect out of this. But on a clinical trial if things are going well, generally speaking, we try to stay on the drug and try to get the maximal benefit for the patient and also to really learn how long it lasts because the only way that we know how long things are going to last is by treating a number of patients for a long period of time.

So I'm glad things are going well, but the question is one that that's one of the things the clinical trial is designed to answer, how long things will work, and we look forward to hearing more about that.

***Mabel Maia***

Thank you, Jennifer, for calling in on behalf of your mom. Our next question comes from the Web. "What do you consider to be old versus younger patients in mantle cell? Is it more about performance status conditions or actual age?"

***John P. Leonard, MD***

So that's a great question and, you know, when people lecture about these topics, they talk about, "Well old is ten years older than I am and young is younger than that." So the older you get, the older you think old is. But at the end of the day, you're correct. The caller raises the issue that it's really not your chronological age. There are 50-year-olds who are in great shape and there are 50-year-olds who may not be in great shape because they have lots of medical problems and there can be 75-year-olds who are in great shape.

Typically speaking, for many of the clinical trials, the more versus less intensive treatment decisions, are framed around the age 65 or so where people over 65 typically are not getting the more intensive treatments and those under 65 are. But that being said, there are no rules in that regard and it's really an individualized decision. It really matters a lot more not only about the chronological age but more so the overall fitness and the overall goals of the patient as to whether or not they are interested in pursuing a more versus less intensive treatment.

***Mabel Maia***

Thank you for submitting that question. Operator, we'll take the next one from the telephone audience, please.

***Operator***

Our next question comes from Judy calling from Pennsylvania. Please state your question.

***Judy***

Thank you. Our son, our young son, has mantle cell and he had a stem cell transplant a couple of years ago with very aggressive treatment and, fortunately, he was in remission for a couple years. It

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has come back and he saw the tumors about six months ago and now they seem to have shrunk some without any treatment. How does that happen? We're thrilled.

***John P. Leonard, MD***

So another great question. In certain types of lymphoma, particularly the indolent lymphomas and occasionally in mantle cell lymphoma, tumors can sometimes shrink without any treatment. And so that's, obviously, something that makes everyone happy and it often raises the question of "Well, what made this happen?" Obviously, if we understood that, we would make it happen much more often than it does on its own.

One possibility is that in some cases, lymph nodes can get bigger for other reasons so that lymph nodes might be getting bigger because the patient has an infection, a virus, some inflammation going on, or some other medical problem and the lymph node swelling is not from the lymphoma but for something else that goes away on its own. So, that is certainly a possibility. If the patient had a biopsy that evaluated that, that would help to rule that in or rule that out.

Sometimes the lymph nodes can shrink on their own. We think that maybe the immune system could be responsible for that or other factors relating to the tumor cells. But if we knew exactly what that was, we would bottle it and turn it into a pill and give it to everybody. So it's an interesting observation, it happens occasionally in patients, and we're always happy when that happens; but I can't say we have a great explanation as to why it happens and what we could do to make it happen more often.

***Mabel Maia***

Thank you, Judy, for calling in on behalf of your son. Our next question is from the Web. "In remission after two treatments of R-CHOP and bendamustine, what could I expect if I choose not to take treatment if mantle cell is apparent?"

***John P. Leonard, MD***

So, in general, R-CHOP and R-bendamustine put people into remission and it typically lasts on the range of about two years or so. We don't typically expect bendamustine-rituximab and R-CHOP to work for five or ten years. Occasionally, that can happen. But, in general, after a few years, the disease comes back and so that's why we are planning for what happens down the line. We sometimes use the maintenance rituximab or a stem cell transplant to try to keep it away longer or sometimes we just watch it and cross our fingers and say when it comes back, "As long as I'm feeling well at this point in time, if it comes back, then we'll deal with it when it comes back with whatever the latest and greatest and most appropriate treatment is at some point in the future." So, in general, that's what we're typically talking about, a couple of years. It doesn't necessarily mean the patient is dying or is sick. It just means the lymph nodes typically start to grow within a couple of years after those treatments. But, again, it really often depends on the specifics of the patient and that's something that I would spend some time with your doctor trying to get a sense of what their expectations would be in that individual situation because it can be variable.

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***Mabel Maia***

Great. Thank you for that question. Operator, we'll take a question from the telephone audience, please.

***Operator***

Thank you. Our next question comes from Vivian calling from Wisconsin. Please state your question.

***Vivian***

I would like to know, I was told I had non-Hodgkin lymphoma (NHL) when I was 87 years old, and I'm doing fine. They gave me a choice of going on a treatment plan, which I chose, and they used Rituxan (rituximab). I had four treatments and I feel fine. I am now 90 years old, but I was wondering what is mantle cell lymphoma?

***John P. Leonard, MD***

Well, mantle cell lymphoma is one of the types of lymphoma. There are a number of different types of lymphoma and mantle cell lymphoma can respond to rituximab treatment, but you may also have a different type of lymphoma. It is not the most common type of lymphoma, but there are various types that can respond to rituximab treatment. So, it sounds like you're doing well. I would suggest that you speak with your doctor to try to get a little bit better sense of which of the different lymphoma types that you have so that you know a little bit more about what to expect from it. But it sounds like you've had a good response to treatment and, hopefully, you'll continue to do well.

***Mabel Maia***

Thank you, Vivian, for calling in with that question. And, actually, thank you all for your questions.

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### **CLOSING REMARKS**

***Mabel Maia***

#### **[Slide 27 – Mantle Cell Lymphoma – Understanding Your Treatment Options]**

We hope this information will assist you and your family in your next steps. If we were not able to get to your questions, please call The Leukemia & Lymphoma Society information specialists toll free at 1-800-955-4572, or you can also reach us by email at [infocenter@lls.org](mailto:infocenter@lls.org). Our specialists can provide you with information about mantle cell lymphoma research and clinical trials and other questions you may have about treatment and financial assistance.

Please help me thank Dr. Leonard. We are so grateful he has donated his time with us today. On behalf of The Leukemia & Lymphoma Society, Dr. Leonard and I would like to thank you for sharing this time with us. Good-bye and we wish you well.