Slide Transcript
Diagnosing and Treating Mantle Cell Lymphoma
March 25, 2015
Speaker: Sonali M. Smith

Slide 1. Welcome & Introductions

Program Operator: Greetings and welcome to the *Diagnosing and Treating Mantle Cell Lymphoma* telephone and web education program. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you Ms. Figueroa-Rivera. You may begin.

Lizette Figueroa Rivera (LLS): On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you. Special thanks to Dr. Sonali M. Smith, for sharing her time and expertise with us today. We have over 350 people participating from across the United States and several countries around the world including Canada, Greece and Libya. Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's Junior Vice President of Research, Dr. Rick Winneker, who will share a few words. Rick, please go ahead.

Dr. Rick Winneker (LLS): Thank you Lizette. I'd like to add my welcome to the patients, caregivers and health care professionals attending the program today. The Leukemia & Lymphoma Society exists to find cures and insure access to treatment for blood cancer patients. Our vision is a world without blood cancer. For more than 60 years, LLS has helped pioneer innovation such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients. To date, we have invested over one billion dollars in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

In addition, as this program demonstrates, we are the leading source of free blood cancer information, education and support and we touch patients in their communities through our 58 chapters across the United States and Canada. LLS also acts as the voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them navigate their cancer treatments and insuring that they have access to quality, affordable and coordinated care.

Slide 2: Title Slide
We are very fortunate to have as our presenter today, Dr. Sonali M. Smith, one of the nation's leading experts in lymphoma. We appreciate her dedication to supporting our mission and her commitment to caring for patients living with blood cancers. I'd like to thank her for providing us today with important information on mantle cell lymphoma. Thank you all and now I'll turn the program back to Lizette.

Lizette Figueroa Rivera (LLS): Thank you, Rick. We would like to acknowledge and thank Takeda Oncology for support of this program. Please complete the evaluation for today's program at www.LLS.org/mcleval or complete the form in your packet.

I am now pleased to introduce Dr. Sonali M. Smith, Director of the Lymphoma Program at the University of Chicago in Chicago, Illinois. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise. Dr. Smith, I am now privileged to turn the program over to you.

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Slide 3. Agenda Slide
Sonali M. Smith, MD: Thank you so much, Lizette and I'd also like to add my warm welcome to everybody who is on the call and to thank Lizette, Dr. Winneker and The Leukemia & Lymphoma Society for the opportunity to share some information about mantel cell lymphoma so that we can all learn and have a better educated understanding of this disease.

I am going to go ahead and start and I am hoping that my slides are coming through appropriately and just start with our agenda. It is actually a very full agenda and I do want to leave some time for questions at the very end but, briefly, we will cover criteria for diagnosing mantle cell lymphoma, what to consider when planning treatment, current treatment approaches and interventions, what patients should know about clinical trials for mantle cell lymphoma and communicating about the quality of life issues with your healthcare team.

Slide 4. What is lymphoma?
Sonali M. Smith, MD: Although there are probably many people on the line who already have a good understanding of lymphoma, I think it is helpful to take a step back and provide a definition of the disease. Lymphoma, or non-Hodgkin lymphoma is basically the name applied to a family of blood cancers, all of which come from white blood cells called lymphocytes. In general, these are cancers of either B-cells, T-cells or NK-cells and by definition these are all cells of our immune system. Their normal job is to fight viruses, bacteria, fungi and foreign organisms. However, when they turn into a cancer we give them this name, non-Hodgkin lymphoma.

Slide 5. Lymphatic system: where the cells of the immune system work and travel?
Sonali M. Smith, MD: Now, most people know about the circulatory system but there is also a lymphatic system, which is a system that is in parallel to the blood system and this is where the lymphocytes travel. The cells can grow in different places within the lymphatic system, called lymph nodes, or they can grow outside of the lymph nodes in which case we use the term "extra-nodal sites." A diagram of the lymphatic system is on this slide and I'll just say that we have a lot of lymphoid tissue in our bodies. Now, normally lymph nodes are part of the immune system, as we mentioned and their job is to enlarge and become painful with infection and this is a sign that the infection is being fought off by the cells of the immune system.

When we have lymphoma, you can have the lymphoma cells grow in any one of these lymph nodes or in the non-lymph node structures and, as you can see, we have the lymphatic system throughout our entire body. Some people often ask whether or not the spleen is considered part of the lymphatic system or not and, as you can see on the diagram here, the spleen is part of the lymphatic system and I often refer to this as basically being a gigantic lymph node although the spleen has some other function as well.

Slide 6. MCL is an uncommon type of non-Hodgkin lymphoma
Sonali M. Smith, MD: So, non-Hodgkin lymphoma is, as we said, a family of blood cancers that are derived from B-cells, T-cells and NK-cells. If we look at all the different diseases that are within this umbrella term, there is actually about 60 different kinds. Importantly, in order to make the best management plan for our patients, we have to know exactly what kind of lymphoma somebody has and then do something called staging. When we look at the entire pie of lymphoma, mantle cell of

lymphoma is a relatively uncommon type of non-Hodgkin lymphoma and accounts for approximately 5% to 6% of the 80,000 new cases that are diagnosed each year in the United States.

Mantle cell lymphoma, although it is relatively uncommon, I think has a very unique position within lymphoma and people have been able to identify it as a unique disease now for about 30 years and this has led to a better understanding and appreciation of who gets this disease and, in fact, the treatments that we'll talk about today are very highly tailored to this particular type of non-Hodgkin lymphoma.

Slide 7. Who gets MCL?
Sonali M. Smith, MD: When we look at who gets mantle cell lymphoma, we have already said this is a relatively uncommon disease. About two to three people per 100,000 in the US population get this disease and that translates to about 3,000 new cases in the United States and perhaps 4,000 in the entire European Union. There is a very unique predisposition in that men have a much higher incidence of mantle cell lymphoma so if you look at some of the data that has been published, the ratio of men to women is somewhere between 3:1 or 4:1 and exactly why that is, is really a mystery. I don't think that women with mantle cell lymphoma get treated any differently based on their biology so it is just an uneven distribution, but really of unclear reason and unclear significance.

Now, this last bullet that is here is that the median age at diagnosis is now estimated to be about 68 years. So when we get into treatment, a couple of things that we keep in mind when we are trying to make treatment plans is that there are both aggressive and less aggressive ways to treat this disease and if we think that the median age is around 68, which is what the data shows, I think that really what that means to me as a physician and as a researcher is that we really need to focus on treatments that are tolerated by the majority of people who have mantle cell lymphoma.

Slide 8. How do patients first come to medical attention?
Sonali M. Smith, MD: Now, in terms of how people first come to medical attention…there is a lot of different ways. I would say, at least in my practice, more and more patients are coming in not because they have symptoms but actually because they have no symptoms. I have had more and more patients who have just had an abnormal blood test and I am going to show you a picture of what a mantle cell looks like traveling in the blood. Or, because we know that mantle cell lymphoma likes to go to non-lymph node structures or extra-nodal sites, that sometimes it is found during a colonoscopy. Some people do have symptoms and if they do, the types of symptoms they can have are that their lymph nodes are larger and don't seem to go away, they might have organ enlargement…for example, the spleen may get very large which can cause pain or pressure. Sometimes if the spleen is getting very large, very quickly you can actually have something called a splenic infarct. What that refers to is a sudden cutoff of blood supply to part of the spleen. You've heard of heart attacks or a myocardial infarct. This is the same type of thing that can happen in a spleen and the way that patients feel it is that they have very sharp and sudden pain usually on their left side or in their left back. Other people can have low blood counts and if your hemoglobin is low sometimes that will lead to fatigue and so that is a very common presenting symptom. And then, rarely, people will have something called B-symptoms.

B-symptoms are a group of symptoms…fevers, night sweats and weight loss…that were classically described with a variety of other lymphomas. I would say that for mantle cell lymphoma this is not nearly as common but certainly, it is a general way in which people with lymphoma may come to medical attention.

Slide 9. How is lymphoma diagnosed?: TISSUE IS THE ISSUE
Sonali M. Smith, MD: Now, the next couple slides focus on how to make the diagnosis and I think as I was eluding to in that pie slide, there are so many different kinds of lymphoma. I think it is very important that both you and your physician feel comfortable that you know which lymphoma you are dealing with because that really helps determine the treatment. So, when it comes to different types of making the diagnosis, I just put a couple of different biopsy types here. People can have a fine needle aspirate, a core needle biopsy or actually an incisional or excisional biopsy which refers to removing part of a lymph node and I would say that the pro of doing a fine needle aspirate is that it is quick, it is easy and it is office based and it will very quickly tell you that this is lymphoma versus something else. However, you don't get a lot of information about the types of cells that are there and when it comes to prognosis…which is trying to predict how well or how poorly a person might do…this is not enough tissue and as you get to larger and larger pieces, you can get much more of that information although the cost in terms of a personal cost is that sometimes in order to get the biopsies this may be more invasive and may require surgery or anesthesia. So, these are things to discuss with your physician if the diagnosis is in question.

Slide 10. Cells can travel in the blood
Sonali M. Smith, MD: Now, I told you I would show you…mantle cell lymphoma can travel in the blood and here is the enemy right here in the middle of this slide. Mantle cells are lymphocytes. These are B-cells and when they travel in the blood they are surrounded by a number of red cells here and you can see that it is larger and it has kind of a unique shape and so, for some people, the diagnosis can be made because they see the mantle cell lymphoma cells traveling in the blood and then specific tests are done to confirm that they are mantle cell and not some other type of lymphoma or lymphoid leukemia.

Slide 11. Key diagnostic tests
Sonali M. Smith, MD: I would say that the key diagnostic test for most people is the lymph node biopsy and although you can make the diagnosis just based on the cells traveling in the blood, sometimes having a lymph node biopsy is helpful when it comes to prognosis. Now, not everybody needs this so if you haven't had one it doesn't mean you have to go out and get one but if you do have a lymph node biopsy, there are some pieces of information that we can gain. For one thing, when the lymph node biopsy is done there are different proteins that can be tested for and this is called immunohistochemical stains. That is just another way of saying let's take this lymph node biopsy, slice it onto a slide and put different stains so that we can confirm the diagnosis. And what we look for is a pattern, and the pattern that we look for is that these proteins are positive…CD20, CD19, CD5, FMC7 and cyclin-D1. If those things are all positive…these are all proteins…and CD23 is negative, it really leads us to this diagnosis. We also will often do chromosomal evaluation, which is done with a test called FISH which stands for fluorescent in situ hybridization and again, that is just the name of the test that we do to look

at the chromosomes that are inside the lymph node and if we find chromosome 11 and 14 in this particular rearrangement, then we feel very comfortable that this is the diagnosis. Here is a picture of what FISH looks like. I told you it is fluorescent and so you see these two probes. When you have these two chromosomes put next to each other they come up with a hybrid signal so instead of just green alone or red alone, you are going to see a hybrid and that is what the scientist or the pathologist sees when they are trying to make this diagnosis.

Slide 12. Cyclin D1-negative MCL
Sonali M. Smith, MD: The last slide that I'll just put out there about making the diagnosis is that very rarely we will have some people who don't have cyclin-D1 and cyclin-D1, you remember, is that protein that is very unique to mantle cell lymphoma but sometimes this may not be present and it may still be mantle cell lymphoma so if there is ever a question, I think one thing that is very helpful with any of these lymphomas is to get a second opinion not necessary for the clinical piece, although you may want to do that as well, but also for the pathology. A dedicated hematopathologist, which is a physician who specifically is trained in studying blood cancers, is usually at your nearest university and that will help make the diagnosis.

Slide 13. 3 "clinicopathologic" types of MCL
Sonali M. Smith, MD: In the end, when we have the diagnosis, we end up with three versions of mantle cell lymphoma. So, again, what these all have in common is that they have those proteins in the order that we were talking about. They occur, like we said, in men more than women and in a certain age group. So, when we have all of the diagnostic material and the right clinical picture, we end up with mantle cell lymphoma. Now, three versions of mantle cell lymphoma that we might see are summarized on this page and so you may see these terms in your chart.

The first is classic mantle cell lymphoma, which is what we see in the vast majority of people. Another is something called blastoid mantle cell lymphoma, which basically means that the cells are a little bit larger and a little bit more aggressive looking. And then we have something called indolent mantle cell lymphoma. These first two, classic mantle cell lymphoma and the blastoid variant, are actually treated essentially the same. The management is based on age and the general health of our patient and, in contrast, indolent mantle cell lymphoma is something that is kind of newly discovered so over the last, I would say, five to seven years there has been an observation that some people with mantle cell lymphoma have a very, very slow or indolent course. And the reason that is important is that in some patients, although for most mantle cell lymphoma when it is diagnosed the thought is…let's make a treatment plan and let's move forward with some sort of management…but, for indolent mantle cell this is something where most of the time people have a large spleen and they have some mantle cell lymphoma cells traveling in their blood but they have no symptoms, they have no other areas that are necessarily involved and there is now some good data that for patients who have that particular initial diagnosis may not need treatment right away. It doesn't mean they will never need treatment; it just means that the disease is progressing so slowly that there can be a period of observation without harming a person's outcome.

I have just a few slides that I wanted to mention about prognosis and staging before we get into treatment. And, just to let you know what prognosis is…prognosis is basically the physician and

the provider team looking at a person saying they have high risk, or low risk, or intermediate risk features and based on that we get an idea of prognosis, which is how we think people may do with the standard treatments. I put this here not because it applies to any one person…okay…but because it can be used when you're looking…if you are trying to read up on the literature and you're looking at outcomes you know…of what has been published…it is helpful to know if, on average, the people who are in those clinical trials had high risk, low risk or intermediate disease because obviously a treatment may have different effects depending on…you know…whether or not the patients who were included had the more worrisome features or not.

Slide 14. MCL is a heterogeneous disease: the MIPI
Sonali M. Smith, MD: So, one of the most useful tools for prognosis in mantle cell lymphoma is this thing called the MIPI, which stands for Mantle Cell Lymphoma International Prognostic Index. This is a clinical tool that your physician can use and it looks at a person's age, something called performance status or how functional they are, LDH which is a blood test and the white blood cell count. By calculating their MIPI…and it is not just a simple additive version (you actually have to do a web based calculator)…you can figure out if a group of patients has low risk, intermediate risk, or high risk and so if they have high risk features, in general, the outcome may not be as good as if you have the low risk features but the MIPI is something that you will see.

Slide 15. What is Ki-67?
Sonali M. Smith, MD: The other prognostic tool that has become very important is something called Ki-67 or key sixty seven…there are different ways to pronounce it. And, what this is, is a marker of proliferation. We talked about stains, which are proteins that we look for, and this is very, very similar. It is a stain that we can do on a piece of tissue if you have a lymph node biopsy and, in general, it tells us how fast the lymphoma is growing…something we call proliferation. The higher the Ki-67, the more aggressive the lymphoma and so we use Ki-67 as a prognostics factor. In the future it may be, because it is such a powerful prognostic factor, maybe it is helpful in choosing a treatment. So, for example…and I don't know if this came out as well…but, if you have a very high Ki-67, in general, the disease progresses a little bit more quickly where as if you have a low Ki-67, it won't. Part of the reason I put this here is that I had mentioned the indolent version of mantle cell lymphoma and in that one, almost always the Ki-67 is less than 10% and so, again, it is another support saying this is not a very proliferative lymphoma, they have these features that are pretty good and perhaps we can avoid treatment for a period of time.

Slide 16. Biologic MIPI: adding Ki-67 to the MIPI
Sonali M. Smith, MD: The Ki-67 has been added to the MIPI and so you can see that when it is added to the MIPI sometimes it can be helpful but again, I just want to emphasize down here, prognostic scales are not meant to be applied to an individual…at least not in mantle cell lymphoma…but they are helpful in predicting out comes for a group of individuals.

Slide 17. Staging: how much disease is present?
Sonali M. Smith, MD: Okay, so far we have covered background of lymphoma, making the diagnosis of mantle cell and a little bit about prognosis. The last piece before we get to the

treatment is staging and staging is a very standard way of evaluating cancers. So, when we do staging, what we are trying to figure out is how much disease or how much mantle cell lymphoma is present and the standard tests that we do are CT scans of the neck, chest, abdomen and pelvis. We will do a bone marrow biopsy to see how much lymphoma is there and we will do blood tests, which will tell us the complete blood count, the chemistries, LDH which is another marker that goes up when the lymphoma is acting very aggressively and something called beta-2 microglobulin. Some other tests that might be useful are a PET scan, although there is some controversy about whether or not this really helps for mantle cell, a spinal tap which is also called a lumbar puncture if we have somebody who has a blastoid variant or if we feel that there is some clinical sign or suspicion that perhaps a mantle cell lymphoma has snuck into the fluid around the brain or a colonoscopy or EGD (which stands for an upper endoscopy). This last one I will say…and maybe this will be a question during our discussion…is that mantle cell lymphoma does like to go to extra-nodal or non-lymph node structures and one of the most common places it likes to go to is the GI tract so sometimes people will have a colonoscopy and we'll see multiple nodules or multiple little polyps and when we do the biopsy it shows mantle cell lymphoma. The challenge that comes up is that after you've treated somebody there are no guidelines on how often to repeat the colonoscopy to see if it has cleared or not so this is, again, something that you would need to discuss with your own physician if this is what you have.

Slide 18: Some notes on diagnosis, staging and prognosis
Sonali M. Smith, MD: So, just to summarize this part of the talk, most patients with mantle cell lymphoma are over the age of 60. Again, the average age or the median age is 68. Most people do have advanced stage and so what this means is that…you've probably heard with different cancers we usually say it is stage 1, 2, 3 or 4. Well, unfortunately for lymphoma, if you have even one cell in the bone marrow we call it stage 4 disease and so this can sometimes be very scary when you first get diagnosed and somebody says…Oh, you have bone marrow involvement or liver involvement or GI involvement and therefore it is stage 4…but, what I would ask you to remember is that stage 4 in blood cancers does not have the same meaning as stage 4 in solid tumors like breast or lung cancer. The vast majority, in fact 2/3 of patients with mantle cell lymphoma have bone marrow involvement and therefore, by definition, have stage 4 disease. That does not mean it is not treatable, it does not mean it is not manageable and it does not mean it is a bad prognosis. It is just describing where the lymphoma is located. So, again, most patients do therefore have advanced stage. B symptoms are less than half the patients. Ninety percent do have involvement of their bone marrow, blood, liver or the GI tract. The vast majority of people have lymph nodes, which we call generalized adenopathy, and then very, very rarely people will have some lymphoma in the brain. Again, whether or not you have a spinal tap to look for this is sort of an individualized decision.

I would say that survival is definitely improving and we have a lot of tools now that we didn't have just a few years ago and we'll be talking about that in the next portion of the talk. Again, although I showed the prognostic scales, remember this applies to groups of patients and it is difficult to be accurate for an individual.

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Slide 19. TREATMENT (transition slide)

Slide 20. Types of treatment for MCL
Sonali M. Smith, MD: So, we'll go on to treatment and I will start very, very broad before we get specific and say that when it comes to treatment for any lymphoma or any cancer in general, we usually think of treatments as one of three tools, or three modalities that we have.

The first is systemic treatments, which are things that travel through the blood. Whether it is given by mouth or through an injection, these are things that are meant to travel throughout the body and this can be either chemotherapy, monoclonal antibodies or biologic agents and that is really what we're going to focus on today. Other tools that are available are surgery and radiation and I will just say that surgery and radiation are both what we call local modalities. They only work where you put your knife or where you aim your beam and so they are not used in the main management of mantle cell lymphoma. So surgery is only helpful to help make a diagnosis and radiation can sometimes be used if there are symptoms in a particular area, but it is never used alone. It is almost always used with some type of systemic therapy.

Slide 21. Basic approach to newly diagnosed MCL
Sonali M. Smith, MD: Okay, so let's say we have somebody who has newly diagnosed mantle cell lymphoma. How do we approach this person's management? I will just say the caveat is that I'm not going to talk so much about indolent mantle cell lymphoma for the rest of the talk and it is really going to focus on both classic and the blastoid variant. One of the first things we do is we try to very loosely categorize patients into being either fit or unfit and you'll notice I put this in quotes. And the reason I put it in quotes, is that this is not a scientific designation of who is fit and who is unfit. This is really more of a judgment call that your physician or your team of providers would make. If people are fit, there is a number of different treatments that we would use including R-HyperCVAD. These are all chemotherapy combinations. And then, follow it with an autologous stem cell transplant. On the other hand, if patients are considered not eligible for these aggressive treatments that are part of the fit approach, then we would go to using less aggressive chemotherapy which could be R-CHOP, something called purine analogs or a new chemotherapy drug…or relatively new…called bendamustine. I think what is kind of fascinating is that some of these unfit treatments are actually turning out to be pretty good and so a lot of people that used to be considered for the very aggressive treatments are now actually being considered for R-CHOP or what was traditionally being used for patients in the "unfit" category.

Slide 22. AGGRESSIVE TREATMENT (transition slide)

Slide 23. R-HyperCVAD
Sonali M. Smith, MD: So, just to start with the aggressive treatment. Again, knowing that this is not going to be for the majority of patients that we take care of just by virtue of the median age, I'll go ahead and cover that first. So what is R-HyperCVAD? In general, when you see these chemotherapy combinations, each capital letter stands for usually a different drug so the longer the name, the more drugs that are being used. R-HyperCVAD was an intensive treatment that was developed at MD Anderson Cancer Center and it has got two portions. The first portion is the CVAD portion, which is a combination of three chemotherapy drugs plus steroids, so

cyclophosphamide, vincristine, doxorubicin plus the steroid called dexamethasone and that alternates with the Hyper portion which refers to methotrexate and cytarabine. The advantage to this particular combination is that it is very, very intense. Both methotrexate and cytarabine can treat lymphoma that is in the brain, which many of our other chemotherapy drugs cannot and using this very aggressive regiment there are actually excellent responses. So, in general, about somewhere between 70% and 80% of people will go into remission and sometimes these remissions can last for a very long time, so I would say these are excellent but it is unfortunately still not a cure and even 10 years later, people who have had R-HyperCVAD may have the disease come back. The other challenge with HyperCVAD or R-HyperCVAD is that there is a lot of side effects especially when you first start this. So, if somebody is over the age of 60, sometimes people can have major complications including infections and that leads to what we call a 4-6% mortality rate meaning that is the percentage of patients if it is applied to a general group of people that may not survive the aggressive chemotherapy. The other issue that is important is that if you get through all eight rounds, we don't usually do a stem cell transplant to hammer home the results…and I am going to talk about stem cell transplant in just a couple of slides.

Slide 24. R-HyperCVAD/MTX/Ara-C in first-line MCL phase II, long-term results
Sonali M. Smith, MD: So, here is what I was talking about in terms of R-HyperCVAD by age. If you look at all ages, 87% of people go into a complete response. I mean, that is a very, very high response. By eight years, 60% of people have had their disease come back and 43% of people have remained in remission. If you look at the breakdown by age, if people are younger their overall survival…eight year survival…is much better than if they are over 65, and I think that has to do with some of the side effects that come with this particular type of treatment.

Slide 25. If intensive chemotherapy has high response rates, but doesn't last – What about consolidation?
Sonali M. Smith, MD: If intensive chemotherapy has very high response rates but doesn't last, what else can we do? Here is where this concept of consolidation comes through. So, if we think about again…remember we are focusing on aggressive therapy, we are focusing on fit patients and we are thinking…okay, with aggressive chemotherapy we can get people into remission. Is there anything we can do to keep them there? And that concept of consolidation has led to the structure where autologous stem cell transplant can be used to hammer home the results that are obtained with some type of induction regimen. In other words, if we are going to be aggressive, we can use one of these chemotherapy regimens and then hammer home the results with an autologous stem cell transplant.

Slide 26. Choice of induction of chemotherapy may make a difference
Sonali M. Smith, MD: What an autologous stem cell transplant really means…it is basically a fancy way of giving high doses of chemotherapy. There is a theory, and this has been shown actually in studies and models that were done in the 1970's and 80's, that the more chemotherapy you give a lymphoma or expose a lymphoma to, the more lymphoma you kill. However, the bone marrow, which is where the stem cells live, can't tolerate the very high doses of chemotherapy so in an autologous stem cell transplant, what we do is give very high doses of chemotherapy and then rescue a person with their own stem cells from the high doses of chemotherapy. When we do this, there are actually very, very long response durations. In fact, sometimes 10 years, 12 years and sometimes even longer

and so this has led to a lot of enthusiasm for doing the autologous stem cell transplant for people who are young enough and fit enough. When it comes to how you get patients to the transplant, there is some data today that using something like R-DHAP, which is a different chemotherapy regimen than R-CHOP, might be a little bit better and that is the blue line here. So, if you are going to go for a transplant, the choice of how people get into remission before that might be very, very helpful.

Slide 27. The most important factor may be minimal residual disease (MRD)
Sonali M. Smith, MD: The other piece that is very important prior to going through a transplant is something called the molecular response. So, we've gotten pretty good as a medical profession to be able to tell if people have leftover disease. We can examine people and say if they have lymph nodes or not, we can do a PET scan and say their lymph nodes are lighting up or not, we can look in the blood and we can look in the bone marrow. But what is even more sensitive, is this concept called minimal residual disease and what this does is it takes cells, usually from the bone marrow, and subjects them to very sophisticated testing that can detect cells that are even one in a million and if people have achieved a molecular response then the chance of people living longer seems to be better so this is something that is actively being investigated. It is not a part of routine care right now but I do think, in general, for people to get the most benefit from a stem cell transplant, we want them to have no minimal residual disease and that is the approach that we would take.

Slide 28: LESS AGGRESSIVE TREATMENT (slide transition)

Slide 29. R-CHOP alone: high response rate but not long-lasting
Sonali M. Smith, MD: I will switch now to the less aggressive treatment and again, noting that this is where most of the patients actually fall in. So again, we come back to…If we have somebody with newly diagnosed mantle cell lymphoma and we decide that they are not somebody who is appropriate for these intensive therapies that have high reward but also high risk, what about chemotherapy?

I'll start out with a combination called R-CHOP. R-CHOP is a chemotherapy combination that has been around for a long time. We use it in a lot of other lymphomas including the most common lymphoma, diffuse large B-cell lymphoma. R-CHOP is a combination of five drugs…rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone. There are actually a number of different studies that have been done showing that R-CHOP has a very high response rate. I just kind of put three cartoons here representing the three studies that I am referencing. What I want you to focus on are the orange boxes here. R-CHOP, if you look at overall response rate, which is the ORR that is here…is very high. It is in the 80% to 90% rate so a lot of people have an excellent response. However, one of the challenges with R-CHOP by itself is that it doesn't last as long so here, this one lasts 21 months, this one lasts 23 months, this one lasts 34 months. R-CHOP by itself is very active but it doesn't last as long as we would like.

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Slide 30. What about adding maintenance rituximab?
Sonali M. Smith, MD: So, one of the key steps forward that has happened in the last couple of years is the concept of adding maintenance rituximab. Rituximab, I think many people may be familiar with. This is an antibody treatment that is very, very active. It attacks a protein called CD20 that lives on the lymphoma cells, goes in by vein and it attacks just those CD20 positive cells and by itself rituximab does not cause nausea, vomiting, hair loss…it does have some other side effects which I am going to get to in a moment, but in terms of trying to…if you get somebody into remission and you want to maintain that remission, maintenance rituximab has been evaluated. What this study, which was done in Europe, looked at is that they took patients with newly diagnosed mantle cell lymphoma and treated them with either R-CHOP or something called R-fludarabine. I put an X here because this particular treatment arm turned out to be too toxic so really what they ended up studying was R-CHOP and then followed by either maintenance rituximab given once every two months or interferon, which is another biologic agent. What these authors found and, again these are just a few curves on the bottom, is that if people got the maintenance rituximab after the R-CHOP they did much, much better. Here if you think about how long the responses last, the median is 75 months which is way more than five years and that is pretty good for something that never required a transplant. You can see if you got R-CHOP and then the rituximab…again, people are doing very, very well and so I think this is an appropriate combination of R-CHOP followed by maintenance rituximab.

Slide 31. Are there risks to maintenance rituximab?
Sonali M. Smith, MD: Now, rituximab is used very often and most people do very, very well with it. There have been some debates over the past as to whether or not there are some risks to maintenance rituximab including low blood counts, perhaps you are going to lose your B-cells for a long period of time, have low immunoglobulins, you might have an increased risk of infection or have a higher risk of activing things like shingles or may not respond to a vaccine as well. This last one, resistance to future treatments I think is always a theoretical concern but I think for an individual these are all issues to talk about with your physician.

Slide 32. What about resistance?
Sonali M. Smith, MD: So…resistance. Not everybody responds to rituximab the first time and some people do end up becoming resistant. If that happens, we use the term called rituximab refractory and we don't know why this happens but it is a theoretical concern and, again, something that I would just encourage you to talk to your physician about.

Slide 33. A "new" chemotherapy: bendamustine
Sonali M. Smith, MD: Now, is there anything other than R-CHOP that we can use? Well, bendamustine is a "new" chemotherapy drug. I put new in quotes because actually this has been available in East Germany decades before it was available in Western Europe or the United States and this is a chemotherapy drug that is very unique. It has got a couple of different parts to it. I am just showing you the chemical structure for fun, not because I know anything about the chemistry, but just to show it has got two different parts to it that may work in complimentary ways. Bendamustine plus rituximab is a whole lot easier than R-CHOP. One of the things with R-CHOP is that the chemotherapy drugs that are used there do cause hair loss and they do have some effects on the bone marrow that increase the risk for infection and so a group of

investigators said…Well, bendamustine is another chemotherapy drug that, for whatever reason, is much better tolerated. Should we see if bendamustine and rituximab is at least as good as R-CHOP? And this was a very large study that was done in Europe and the final results have been published and what it showed is that for mantle cell lymphoma at least, bendamustine and rituximab was better than R-CHOP. Now, remember that nobody in the study had maintenance so R-CHOP plus maintenance may actually be very similar to bendamustine and rituximab but that type of study has not been done. But I think what it tells us is that bendamustine plus rituximab is a very, very appealing and appropriate option. If you look at the side effects, one of the key issues is that bendamustine and rituximab is significantly less toxic when it comes to the risk of infection, low blood counts and hair loss. I won't say that there isn't any infection or low blood counts; certainly that is a concern, but the numbers at least when compared to R-CHOP seem very, very reasonable.

Slide 34. Is BR better than R-CHOP?
Sonali M. Smith, MD: Another thing that is kind of new, and I just wanted to point this out because it got some press, is that there is a drug called bortezomib and bortezomib is a drug we'll talk about in just a few minutes, that has been very active in people who have already been treated for mantle cell lymphoma and so many people are trying to bring it up into the front line setting and so here is a way of trying to reduce toxicity by using some of these newer drugs. I am just going to kind of move forward a little bit because I want to make sure we have enough time for questions but just to say that this is a variant of the Hyper-CVAD that we had talked about that may be a little bit less toxic.

Slide 35. Agents in the relapsed setting now being tested in initial treatment
Sonali M. Smith, MD: Alright, so now what about drugs in the relapse setting? We have now a number of different drugs that are FDA approved including bortezomib, lenalidomide, mTOR inhibitors, ibrutinib and GS-1101 and these drugs are now approved. They have different response rates that are shown here and different response durations and I am going to walk you through some of these but the main thing I wanted to say is that because these drugs are so active in the relapse setting, they are now being tested in the front line setting.

Slide 36. LYM-3002: Replace vincristine with bortezomib
Sonali M. Smith, MD: So, bortezomib is the first drug ever FDA approved for relapsed mantle cell lymphoma and what this European primarily Italian group did is, they said…Well, let's look at R-CHOP. R-CHOP is good but, like we've talked about, it doesn't last as long. We know that bortezomib is active in the relapse setting. Why not move it up and replace the vincristine, which is the O here, with the bortezomib?

Slide 37. Superior PFS by IRC with VR-CAP vs R-CHOP: 59% improvement
Sonali M. Smith, MD: And they presented this just this past year, so this is very cutting edge, and what they found is that if people received the bortezomib containing treatment they actually did much better than R-CHOP and this is how long. This is progression-free survival, which means how long people go without their disease progressing and it is much, much better if people get the bortezomib containing treatment. So, this is now actually part of our NCCN (National Comprehensive Cancer Network) Guidelines and is FDA approved to be used instead

of R-CHOP if that is considered appropriate for people in the front line setting. Now, importantly, there has been no difference in what we call survival, which means how long people live, but I think a lot of that has to do with the fact that the study needs to be followed for a long period of time so that we know not just in two or three years, but five or ten years what is the impact…so I would say to stay tuned.

Slide 38. Peripheral neuropathy
Sonali M. Smith, MD: Now, one of the most important side effects to bortezomib is something called peripheral neuropathy which is an irrigation of the nerves. Sometimes it can be very troublesome and cause people to lay awake at night with pain or numbness and this is obviously something that is very important for us to try to avoid if we can or minimize. What the authors did is they looked at the percentage of people who developed peripheral neuropathy in those who got R-CHOP, which is very standard or the VR-CAP and they found it was pretty much the same…29% versus 30% and maybe just a little bit more in terms of serious neuropathy for those people who got the bortezomib but certainly very comparable and, again, speaks to the fact that this is an appropriate option.

Slide 39. Lenalidomide/rituximab in frontline MCL: R2 regimen
Sonali M. Smith, MD: Now, the last sort of front line thing I wanted to talk about is that there is also a move to try to get away from chemotherapy altogether. Can we just use biologic agents? Here is again sort of a cutting edge abstract and this has been presented a number of times and I think is going to go forward, which is to say lenalidomide which is a drug that is FDA approved in the relapse setting…why not use it up front with rituximab and because lenalidomide has a trade name that starts with an R, they are calling it the R squared regimen. This particular study, which is from Cornell, looked at lenalidomide plus rituximab. Lenalidomide is a pill, combined with rituximab and there is both an induction portion and then there is a maintenance portion of these two drugs.

Slide 40. R2 in MCL: Progression-free survival
Sonali M. Smith, MD: By doing that, so far early going, but it seems like the overall response rate is very high and …again, this is kind of short follow up…most people are still doing well. So, again, something to sort of stay tuned and of course this is also an option for people who have had mantle cell lymphoma that has come back.

Slide 41. WHEN MCL COMES BACK (transition slide)

Slide 42. Approved agents for relapsed MCL
Sonali M. Smith, MD: Alright, so speaking of mantle cell lymphoma when it comes back, this is also called recurrent or relapsed disease. I would say that there are now a number of agents that are now FDA approved for relapsed mantle cell lymphoma. We have chemotherapy drugs, we have monoclonal antibodies, we have biologic agents, bortezomib, lenalidomide, ibrutinib and in Europe at least, there is temsirolimus, which is an mTOR inhibitor.

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Slide 43. New agents on the horizon…
Sonali M. Smith, MD: There is also a ton of new agents on the horizon and these include Bcl-2 inhibitors, BTK inhibitors and the list goes on and on and on. I would say the one theme that is pretty cool about all of these is that many of them are oral so that you don't have to be in an IV therapy chair, which I think is always much nicer if you can take it at home. As long as people stick to it and take the pills the way they are described I think that is the way we'd like to move in the future.

Slide 44. Bortezomib is the first drug FDA-approved for relapsed MCL
Sonali M. Smith, MD: So, bortezomib we already kind of talked about. This was the first drug FDA approved for mantle cell lymphoma and I just kind of put this slide here to say about 1/3 of patients respond and if the response is a complete response, the response typically lasts somewhere between one and two years, and a lot of the new drugs that are being evaluated are going to be held against this particular benchmark.

Slide 45. Immunomodulatory agents: seed vs. soil
Sonali M. Smith, MD: Now, the next class of drugs that was FDA approved are those called immunomodulatory agents and I think the best way to think about immunomodulatory agents is that they attack not only the cancer cell, which we can think about as the seed, but also the soil which is all the cells that nurture the cancer cell and so when we give an immunomodulatory agent, what we end up doing is getting rid of those cells that support the cancer cell as well as its blood supply. And so, if that happens, the cancer cell can no longer survive and we've kind of hit two birds with one stone.

Slide 46. Lenalidomide has many effects on lymphoma and the microenvironment
Sonali M. Smith, MD: The key drug that is thought to be an immunomodulatory agent, or classified as such, is lenalidomide. Lenalidomide has a lot of different effects on what we call the microenvironment…that soil that supports that cancer seed. It helps block off its blood supply, it helps get rid of chemicals that are like vitamins for it and it can also let the immune system now suddenly re-recognize the mantle cell lymphoma as being there.

Slide 47. Lenalidomide in relapsed MCL: MCL-001 (EMERGE trial)
Sonali M. Smith, MD: So, when we look at mantle cell lymphoma and look at the data, this was all FDA approved through the EMERGE trial and it looked at people who had stopped responding to bortezomib and then gave them lenalidomide.

Slide 48: EMERGE Study
Sonali M. Smith, MD: For this group of patients, the overall response rate again is about 1/3 of patients responded and if they responded this lasted somewhere between one and two years. Again, as an oral agent, lenalidomide is certainly attractive that way.

Slide 49: Side effects of lenalidomide
Sonali M. Smith, MD: The side effects to lenalidomide is that it can cause low blood counts, it can cause some fatigue or diarrhea and then one thing that is not on the slide is that it does increase the risk of blood clots so that is something, again, to talk about with your physician if lenalidomide is chosen.

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Slide 50: What are signaling pathways and why do we care?
The last group of drug that I'll talk about, which is probably the most exciting, are drugs that block signaling pathways. Signaling pathways are cascades of events inside of a cell and they are signals that say…these cancer cells need to grow and stay alive. It turns out we can block these signals and, in some cases, the cancer cells are actually addicted to certain pathways so if we get rid of their source they actually don't survive and we leave the normal cells alone.

Slide 51: Signaling pathways: tell cancer cells what to do
Sonali M. Smith, MD: One way to look at a signaling pathway is that protein 1 tells protein 2, which tells protein 3, which tells the cell to grow, divide, invade and spread. When we use a drug that blocks any one of these proteins, we can prevent any of these things from happening.

Slide 52: New targets in MCL
Sonali M. Smith, MD: The signaling cascades that have been the most important in mantle cell lymphoma is something called B-cell receptor signaling and the B-cell receptor is a protein that sits on the surface of the mantle cell lymphoma cells and by using all of these signaling pathways, it tells that cell to survive. What we now have are a couple of drugs, two of which are FDA approved and listed on this slide that can block this signaling pathway. One is idelalisib and the other one is ibrutinib and then I just kind of put a few others in there.

Slide 53: Ibrutinib in Bortezomib-naïve or -exposed MCL: study design
Sonali M. Smith, MD: SO, let's talk about ibrutinib. Ibrutinib is an oral agent, so it is a pill, and it blocks that signaling pathway from B-cell receptor signaling and attacks a protein called BTK. The study that led to its approval was a trial where all patients got ibrutinib 560 mg per day. They got it continuously until they either stopped responding or couldn't tolerate it. This was a group of patients that were very, very heavily pretreated so these are people who have had at least three, sometimes four or five different prior treatments that had stopped working.

Slide 54: Ibrutinib in rel/ref MCL: response by subset
Sonali M. Smith, MD: Lots of different agents had been tried and here comes this pill and what ends up happening, and I'm sorry that this is a little bit small, but the overall response rate in a group of people who h. ad already been treated with a lot was quite high. It was about 72% or 68%. This lasted almost two years or a year and a half with very short followup. I do think that as we learn more about this drug, I think some people actually have very, very long responses with ibrutinib.

Slide 55: Single agent idelalisib in relapsed/refractory MCL
Sonali M. Smith, MD: Similarly, idelalisib is another drug that blocks some of these signaling pathways and this is a drug that is not FDA approved just yet for mantle cell lymphoma but itself although in combination it might be. Here you can see that it has response rate of about 40%. It doesn't last quite as long but, again, we are looking at people who have really been treated quite heavily.

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Slide 56: Finding new lymphoma treatments
Sonali M. Smith, MD: The only way to find new treatments and to really fine tune what we are doing is that we have to do some clinical trials and what we'd like to do is the new drugs that are being developed today, we want them to be smarter, we want them to be targeted and we want them to make sense or be rationale. The way we do this is through clinical trials and I know people get nervous when they hear about a trial…they don't want to be a guinea pig…but I think that there is a lot of different kinds of trials that can either prevent, be used to help diagnose the disease or focus on treatment. There are lots of different kinds of clinical trials.

Slides 57- Slides 66: For your Reference
Sonali M. Smith, MD: I am actually going to pause for a moment, if you'd like me to answer some questions. The last part of the talk was going to focus on "What are clinical trials?"

Slide 67: Concluding thoughts

Slide 68: Thank you!

Slide 69: Question and Answer Session

Question #1 (Lizette Figueroa Rivera/LLS): Thank you. Dr. Smith, the first question is from our online audience. Marian asks: What does the research show about using the CAR-T protocol for mantle cell lymphoma patients?

Answer #1 (Sonali M. Smith, MD): That is a great question. Just for everybody else, what CAR-T stands for is chimeric antigen receptor T-cells and what it is, is you take T-cells from a patient and you engineer those T-cells to suddenly recognize the mantle cell lymphoma and therefore use the person's own immune system to attack the lymphoma. There is actually very, very little data in mantle cell lymphoma in particular…I mean less than 50 people ever treated with a CAR T-cell. I will say it is very exciting but so preliminary that we have nothing that we could synthesize into a slide even for mantle cell lymphoma. People are still working on the dose of the T-cells, exactly how to engineer the T-cells and the timing of how to give it back. I just want to say that this is something that will probably be at last five, maybe longer years away from being routinely used.

Question #2 (Lizette Figueroa Rivera/LLS): We will take the next question from the telephone audience.
(Operator): The next question is from Cindy from Georgia:
I had a question regarding…we haven't talked about it…but GVHD. If there is anything new with controlling or eliminating GVHD, chronic?

Answer #2 (Sonali M. Smith, MD): Thank you very much for that question. GVHD stands for graft versus host disease and I did not talk about allogeneic transplants. Mostly what I focused on was autologous transplant because that is what we use up front. Allogeneic transplant is…you remember we talked about using the person's own stem cells for an auto transplant…so when

you do an allo transplant you use somebody else's stem cells…either a brother or a sister or a cord or an unrelated donor. The advantage to using an allo transplant is that those new stem cells are clean in the sense that they have never been exposed to chemotherapy and they have no mantle cell lymphoma. They also give you a whole new immune system which should be able to recognize mantle cell lymphoma as not belonging and eliminate it. The down side to those new stem cells is that sometimes they can attack the person's own body and cause a second disease called graft versus host disease or GVHD.

GVHD can become very serious and can attack a lot of the normal organs and sometimes that is as challenging, if not more challenging, than the mantle cell lymphoma to begin with. The main treatment is steroids and knocking down the immune system. Sometimes you can use something called photopheresis which can help with the skin complications of graft versus host disease and there are some new immunosuppressants being developed but I would say that graft versus host disease remains kind of a tough disease. It is a challenging situation to manage. The most important thing is to remember that if you have GVHD, your immune system is not normal and your risk of things such as viral infections is very high. The last thing I'll say about GVHD is that on that note, some of the viral infections that have been the toughest to take care of…there are new antiviral treatments so something cidofovir or brincidofovir, which are still in the investigational phases, are becoming very useful to attack some of the viruses that go along with GVHD. Most people who have an allo transplant are already in a university setting but I would say that the infectious disease doctors and the transplant doctors often work very closely together to try to minimize the side effects of GVHD.

Question #3 (Lizette Figueroa Rivera/LLS): The next question, Doctor, comes from the web. It is from Ken. He says…I have MCL and currently on ibrutinib for the past 11 months and doing well. Since several therapies did not work and ibrutinib is working, do they know any more why ibrutinib can become resistant?

Answer #3 (Sonali M. Smith, MD): That is a really great question, Ken, and I'm glad that things are going well for you on ibrutinib right now. I think that is actually the next frontier so that list of drugs that I had put there saying…Here are some future drugs coming by…I think it is because we do recognize that ibrutinib for mantle cell lymphoma may not last forever and there is resistance that develops and some of it is because the protein that ibrutinib attacks mutates or other signaling pathways can compensate for the B-cell receptor pathway being blocked out. If that happens, at our institution we actually have a very strong Molecular Pathology Lab that is trying to understand some of the mutations that occur. We actually just published some of this data as well and I know people around the country are looking to see if they can predict who is going to progress and who isn't on the ibrutinib. For right now, I would say that there are second and third generation BTK inhibitors being developed, there are combinations being developed and this is an area that is very, very actively being investigated.

Question #4 (Lizette Figueroa Rivera/LLS): Our last question comes from Brian. He says he is just finishing two years of Rituxan maintenance and do you recommend periodic CT scans in order to detect any recurrence and if so, how frequently?

Answer #4 (Sonali M. Smith, MD): That is probably one of the most important questions, Brian, which is how do we do surveillance? On a good note, I think mantle cell lymphoma is something that we manage for many, many, many years and sometimes even decades and so we want to keep both the short-term and the long-term view in mind. On one hand, doing scans does tell us what is happening with the disease. On the other hand, it doesn't always help us in terms of what to do next in terms of management because even a small growth doesn't always mean we have to jump in with new treatment right away, especially if people are feeling well. I would say that the guidelines right now are to minimize the number of CT scans. In my practice, I will do this maybe when I first meet somebody and they first finish treatment I will do scans about every four to six months for the first year and then after the first year or two I don't' really get a lot of CT scans unless there is a symptom. The symptoms can be some of the things we talked about way early in the talk or anything that is unusual…fevers, sweats, weight loss…anything else that doesn't quite fit with your usual how you feel could prompt a CT scan but we try not to do too many routine ones because there is a small, but real, radiation risk exposure.

Slide 70: The Leukemia and Lymphoma Society (LLS) offers:
Lizette Figueroa Rivera/LLS: Thank you, Brian, for that question and thank you all for participating in today's program. Please help me thank Dr. Smith for volunteering her time with us today. We hope this information will assist you and your family in your next steps. If we were not able to get to your question today, please call The Leukemia & Lymphoma Society's Information Resource Center at 1-800-955-4572. Information specialists are available to speak with you from 9AM to 9 PM Eastern time or you can reach us by email at infocenter@LLS.org. We can provide information about treatment including clinical trials or answer other questions that you may have about support including questions about financial assistance for treatments.

Please complete the evaluation for today's program at www.LLS.org/mcleval or complete the form in your packet. Continuing education credit is not being offered for this program.

Again, thank you Dr. Smith, for sharing your knowledge with us today. To all of the patients, caregivers and professionals on the program today, on behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us. Goodbye and we wish you well.

TELECONFERENCE END