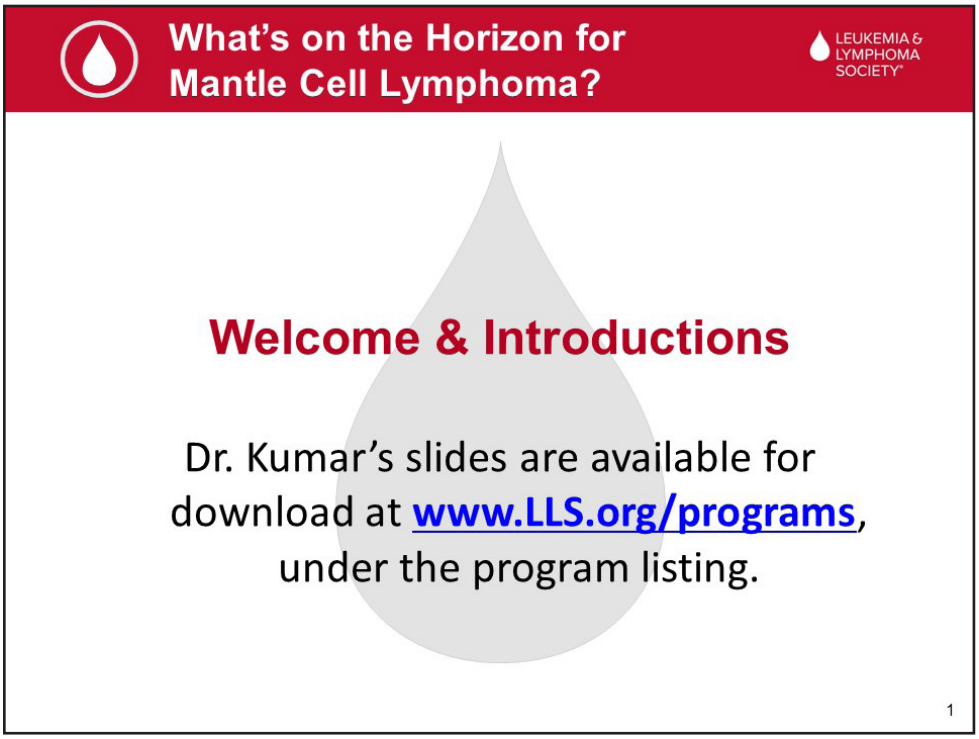


Slide 1. Welcome and Introductions

Lizette Figueroa-Rivera:
Hello, everyone. On behalf of The Leukemia & Lymphoma Society (LLS), I would like to welcome all of you.

Special thanks to Dr. Anita Kumar for volunteering her time and expertise with us today.

Before we begin, I'd like to introduce Karen DeMairo, The Leukemia & Lymphoma Society's Executive Director of Education and Integration, who will share a few words. Karen, please go ahead.

Karen DeMairo:
Thank you, Lizette. I'd like to add my welcome to the patients, caregivers, and healthcare professionals attending the program today.

The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients. Our vision is a world without blood cancers. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

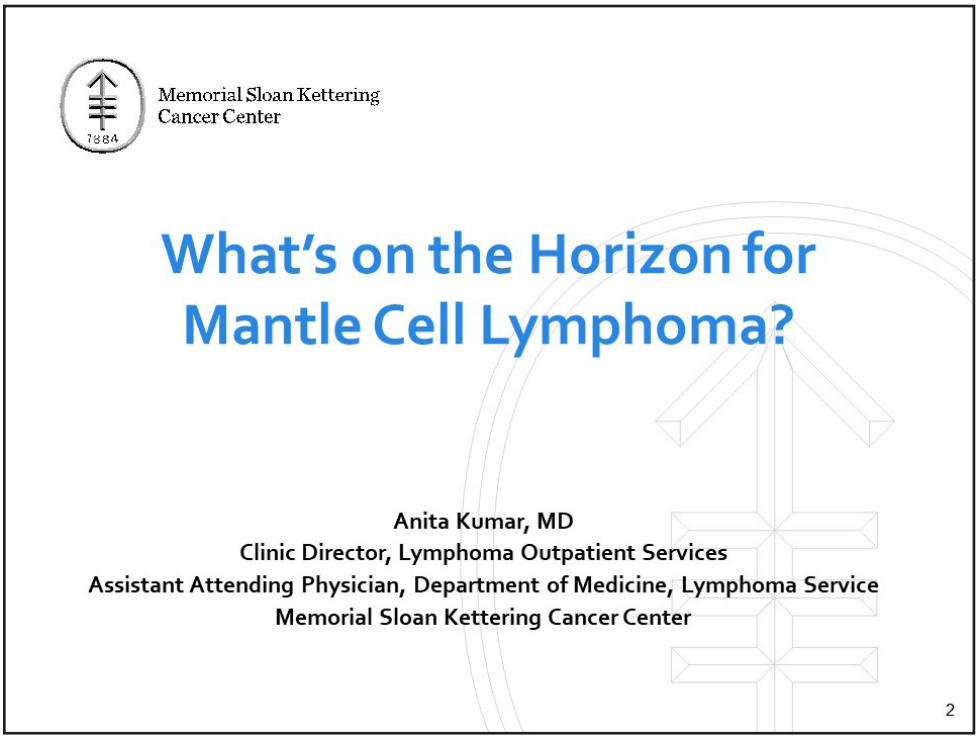
As the world's largest voluntary health organization dedicated to fighting blood cancers, The Leukemia & Lymphoma Society has recently awarded 2 competitive grants to researchers in major institutions through a new program to benefit mantle cell lymphoma (MCL) patients. This is a milestone-driven research program with an overarching goal to move discoveries quickly from the bench to the clinic.

Our *LLS Community* is our online social network and registry for people living with or supporting someone with blood cancer. *LLS Community* is a one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. You can visit us or join us at *www.LLS.org/community*.

We're fortunate to have as our presenter today, Dr. Anita Kumar, one of the nation's leading experts in mantle cell 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:
Thank you, Karen. And we would like to acknowledge and thank AstraZeneca Pharmaceuticals, Celgene, and Pharmacyclics, an AbbVie Company, & Janssen Biotech for support of this program.



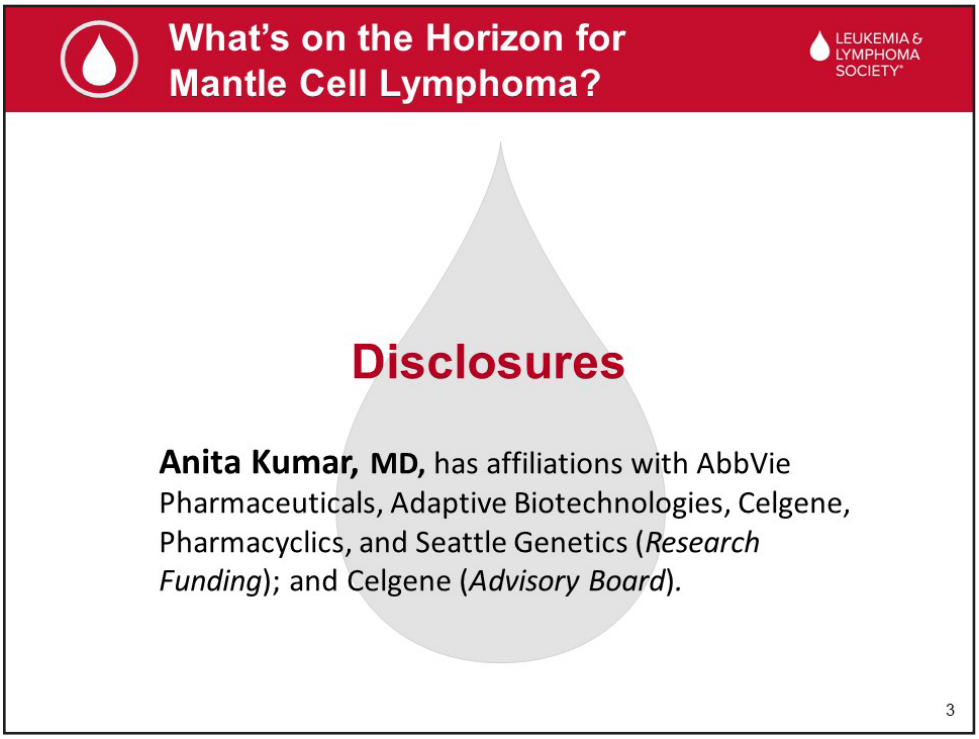
Slide 2. What's on the Horizon for Mantle Cell Lymphoma?

I am now pleased to introduce Dr. Anita Kumar, Assistant Attending Physician of Lymphoma Service at Memorial Sloan Kettering Cancer Center and Instructor at Weill Cornell Medical College in New York, New York.

Dr. Kumar, I'm privileged to turn the program over to you.

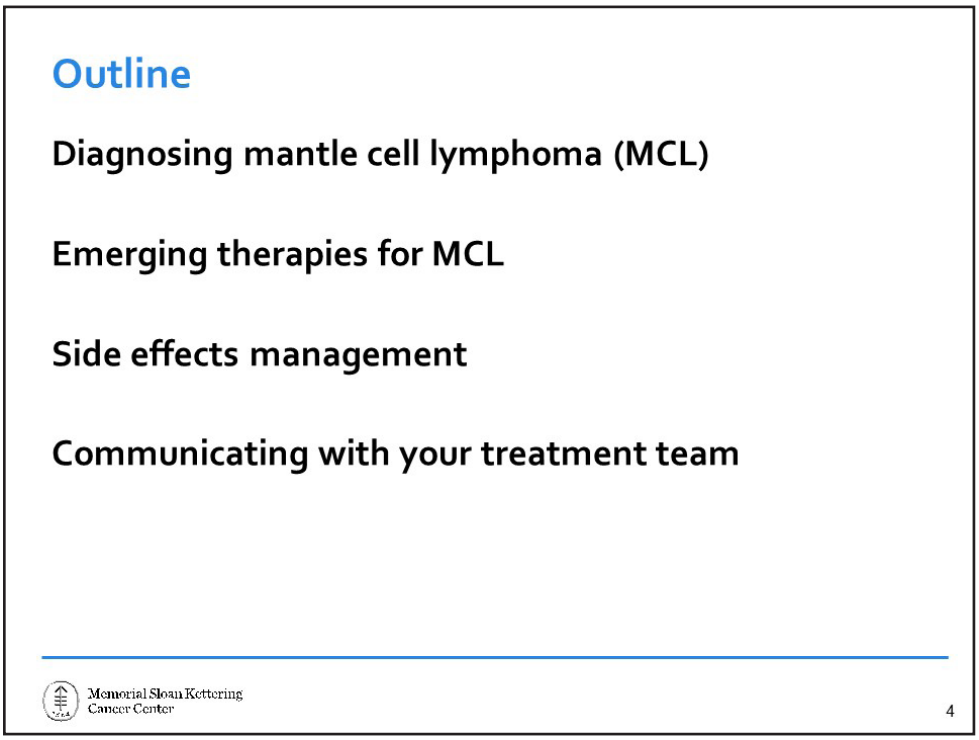
Dr. Kumar:
Thank you, Lizette, and thank you, Karen, and thank you very much to the LLS for this opportunity to speak with you today.

My name is Dr. Anita Kumar and I am a medical oncologist at Memorial Sloan Kettering Cancer Center (MSKCC), with an expertise in mantle cell lymphoma. I am very passionate about improving outcomes for patients with mantle cell lymphoma and am leading a clinical research program incorporating new treatment approaches for patients with mantle cell lymphoma. It is truly an honor and privilege to speak with all of you today about our MSKCC approach to the diagnosis and management of mantle cell lymphoma. Thank you very much for having me.



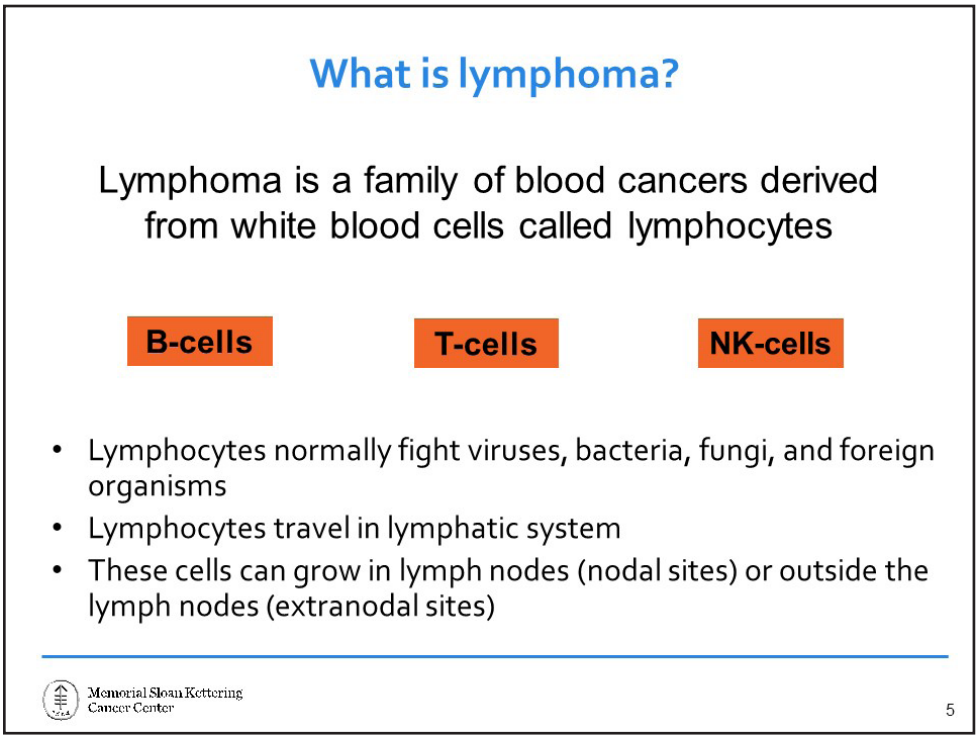
Slide 3. Disclosures

These are my disclosures.



Slide 4. Outline

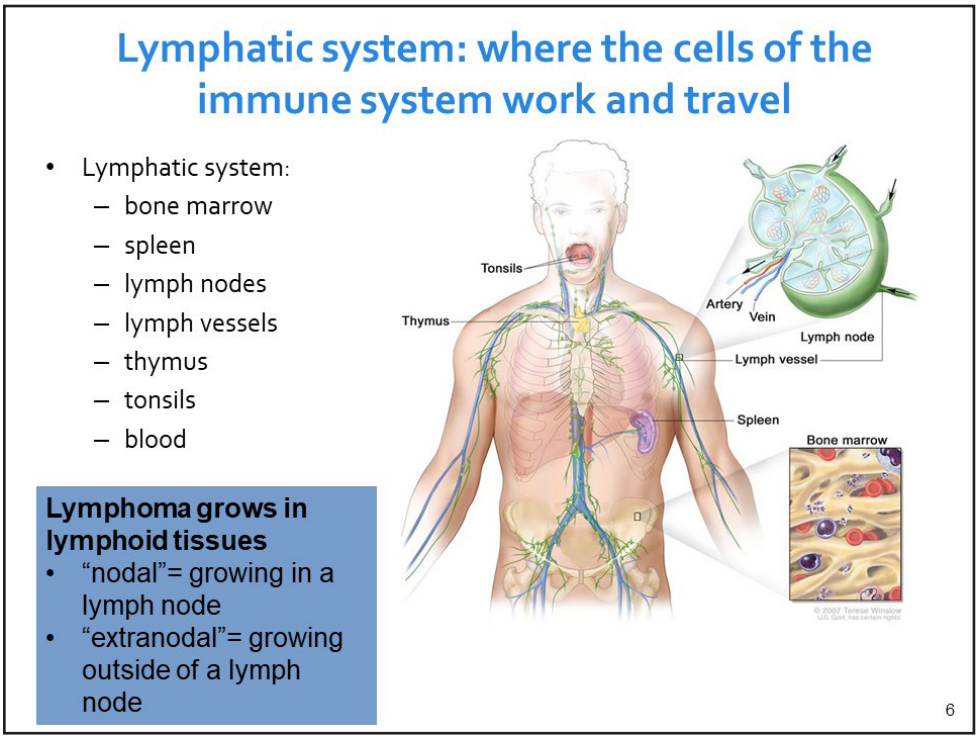
For today's talk, I'll be talking about 4 different areas: one diagnosing mantle cell lymphoma, two emerging therapies for the treatment of mantle cell lymphoma, I'll briefly review some important considerations in terms of the management of side effects of available treatments, and also talk about some tips with regard to communicating with your treatment team.



Slide 5. What is lymphoma?

I'll begin by asking the question, what is lymphoma? How do we think about the classification of lymphoma, and how does mantle cell lymphoma fit within the larger group of diseases of lymphoid malignancies?

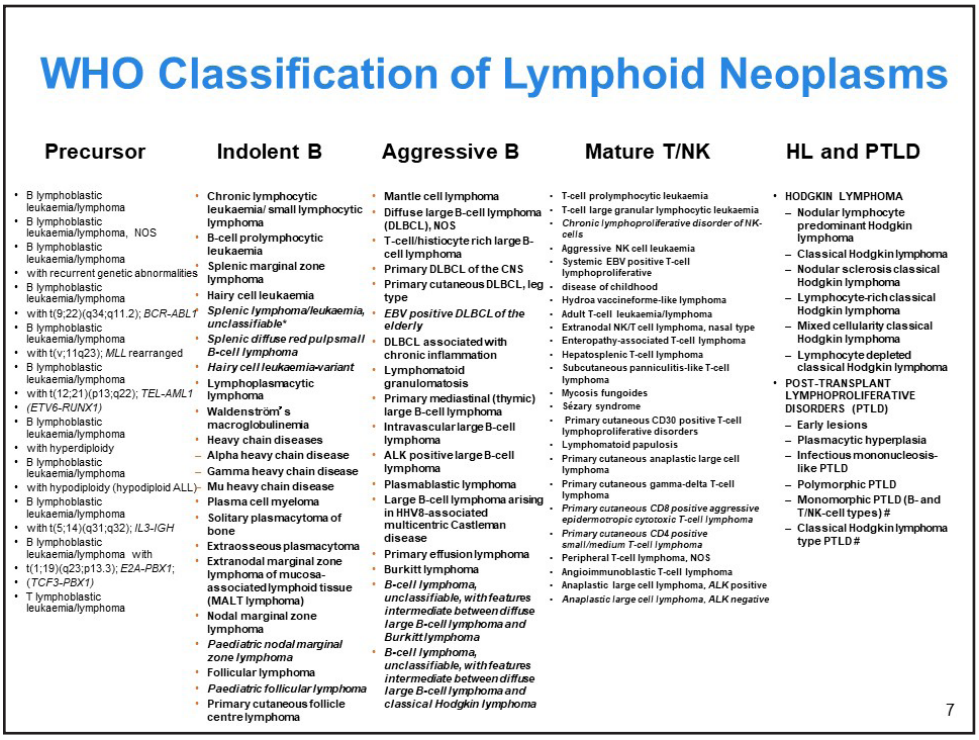
Lymphoma is a family of blood cancers which arise from white blood cells called lymphocytes. There are different subtypes of lymphocytes – B cells, T cells, and natural killer cells. Lymphocytes are an important part of our normal immune system. They usually fight viruses, bacteria, fungi, and other foreign organisms. These lymphocytes travel throughout the lymphatic system and can grow within lymph nodes or outside of lymph nodes.



Slide 6. Lymphatic system: where the cells of the immune system work and travel

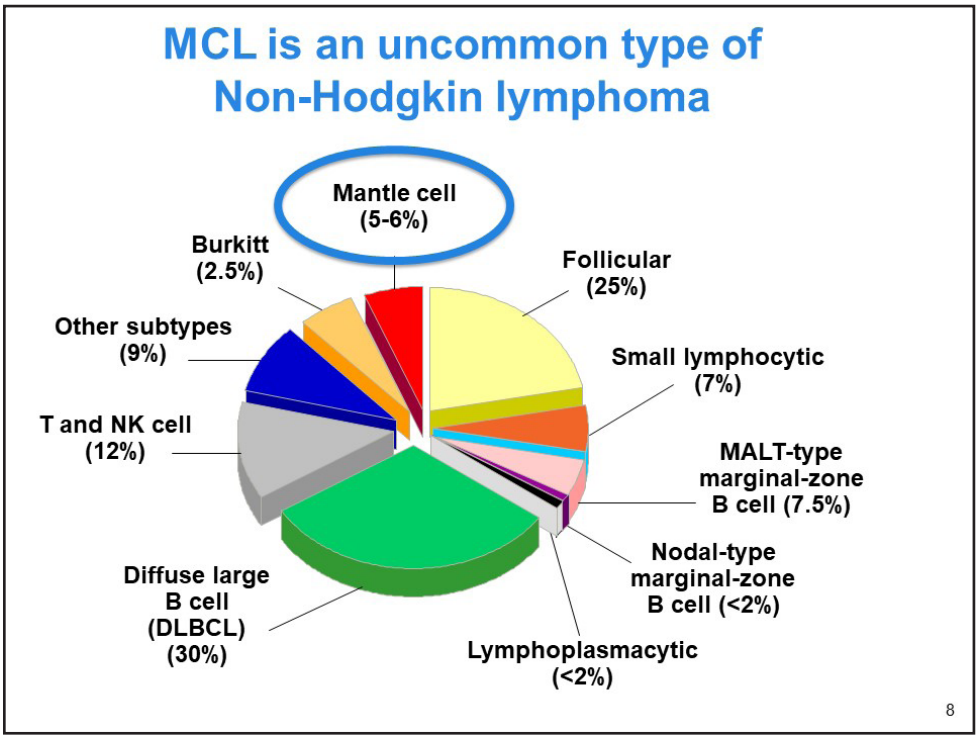
The lymphatic system is the system in which the lymph nodes travel and do their work. There are various organs that are key parts of the lymphatic system: such as the bone marrow, where all of the blood cells are produced, the white blood cells, the red blood cells, and the platelets; the spleen, which is an enlarged lymph node; the various hundreds of lymph nodes that are scattered throughout the body; the lymph vessels; the sinus, which is an immune organ that's more important during childhood and then becomes smaller throughout adulthood; the tonsils; and of course the blood.

As I mentioned before, lymphoma is a disease that can grow within the lymph nodes, but it can also circulate within the blood or grow in extranodal sites, which are those sites outside of a lymph node.



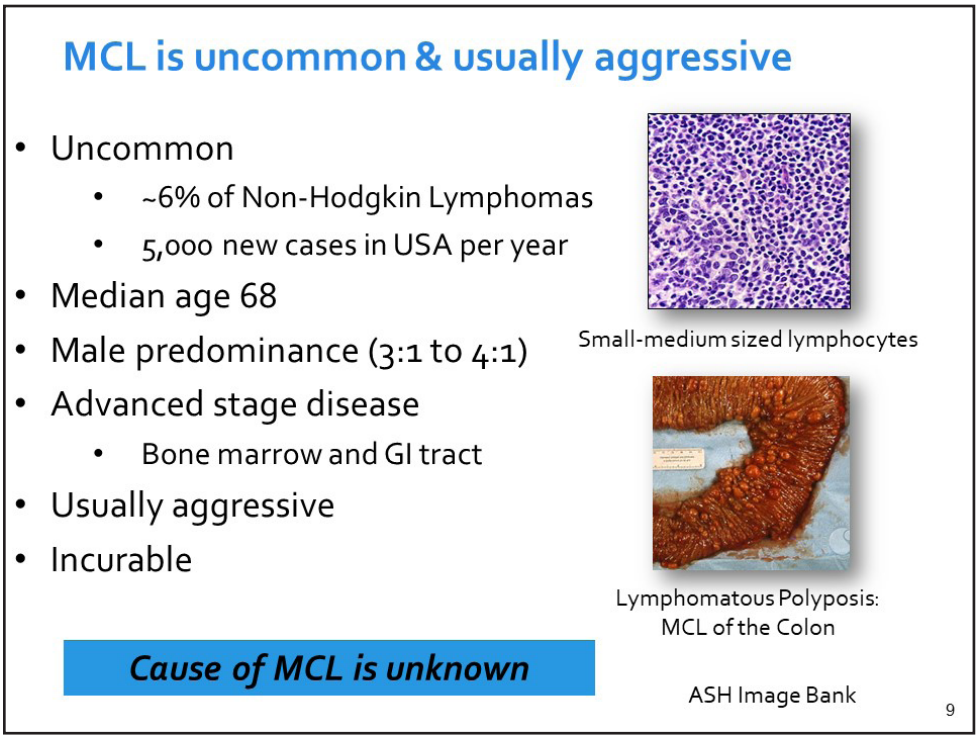
Slide 7. WHO Classification of Lymphoid Neoplasms

There are over 70 different kinds of lymphomas. I put this slide in just to show that there are many, many different subtypes and there's different ways of classifying lymphomas. Mantle cell lymphoma is a specific subtype of B cell non-Hodgkin lymphoma that is typically aggressive.



Slide 8. MCL is an uncommon type of Non-Hodgkin lymphoma

Mantle cell lymphoma is a rare subtype of non-Hodgkin lymphoma. Of all subtypes of non-Hodgkin lymphoma, it represents about 5 to 6% of non-Hodgkin lymphoma.

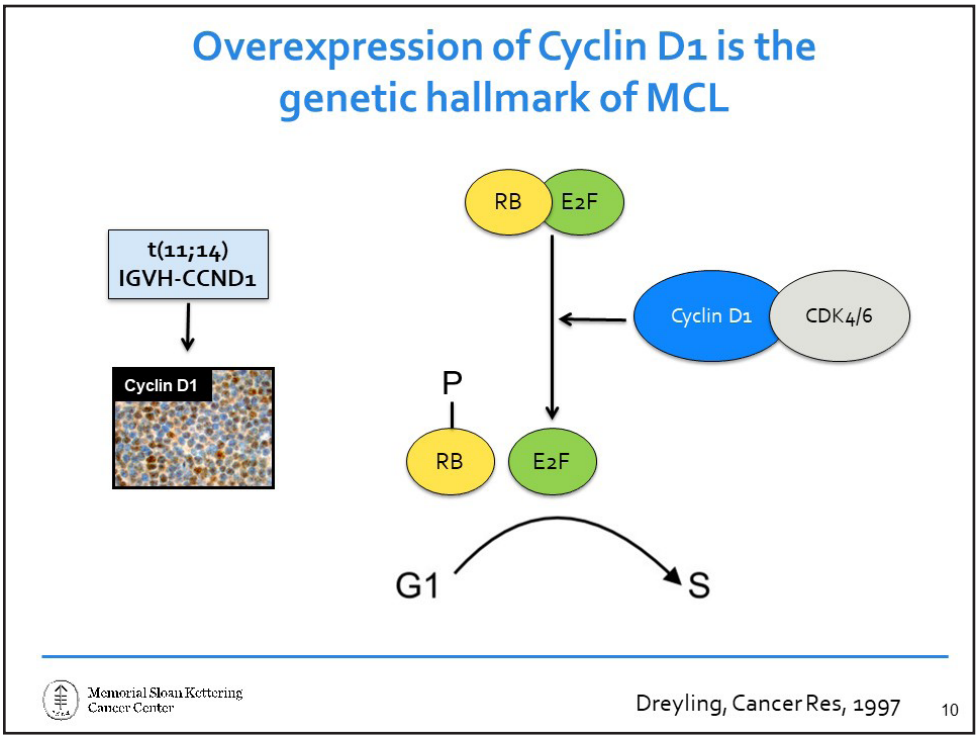


Slide 9. MCL is uncommon & usually aggressive

As I mentioned, mantle cell lymphoma is uncommon. The average or median age at presentation is 68 years. It's more common in men than in women with about 3 to 1 or 4 to 1 predominance in men versus women. It oftentimes presents with advanced stage, meaning it is involving sites that are outside of the lymph nodes. The most common sites of extranodal involvement are the bone marrow or the gastrointestinal tract.

Here on the slide you can see this picture of mantle cell lymphoma involving the colon. This is a rare subtype of mantle cell lymphoma called lymphomatous polyposis, where we see mantle cell lymphoma carpeting the lining of the colon.

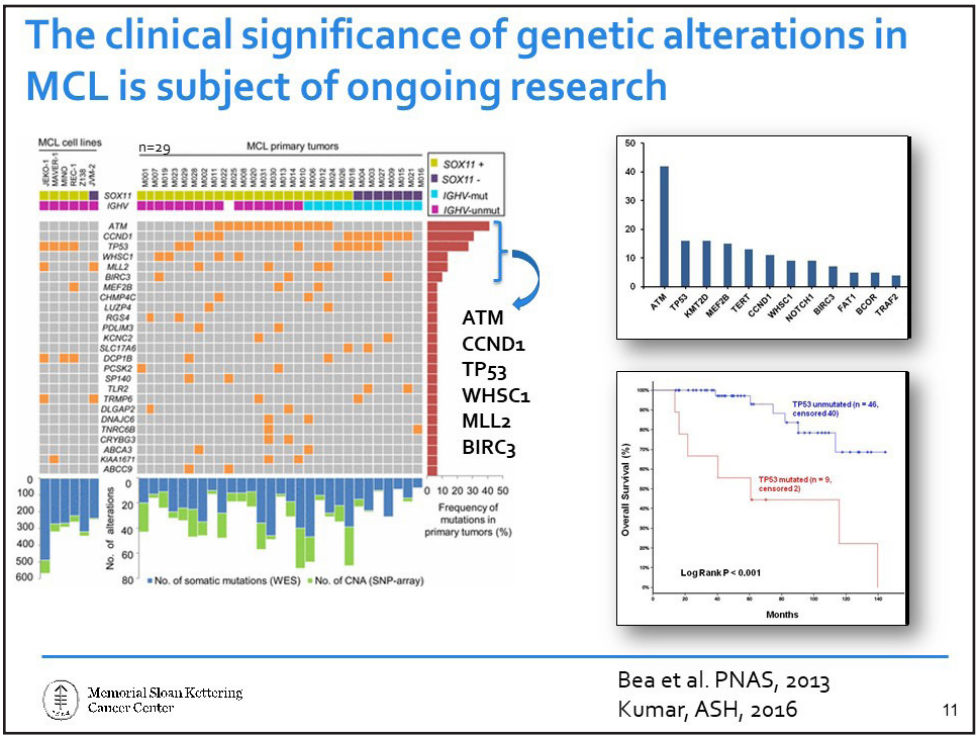
Typically, mantle cell lymphoma is aggressive and at the present time we consider mantle cell lymphoma an incurable disease, but we hope in the future to find a cure for mantle cell lymphoma. And, I'll also highlight that the cause of mantle cell lymphoma is not currently known. There's no clear risk factor that's associated with mantle cell lymphoma and it's not a disease that's passed down within families. Or, in other words, there's not a known hereditary cause for mantle cell lymphoma.



Slide 10: Overexpression of Cyclin D1 is the genetic hallmark of MCL

There is a genetic hallmark of mantle cell lymphoma which involves the coming together in an abnormal way of 2 different chromosomes, 11 and 14. This leads to the increased expression of a protein called cyclin D1. Cyclin D1 is an important regulator of the cell cycle, and increased expression of cyclin D1 leads to increased cell growth and proliferation.

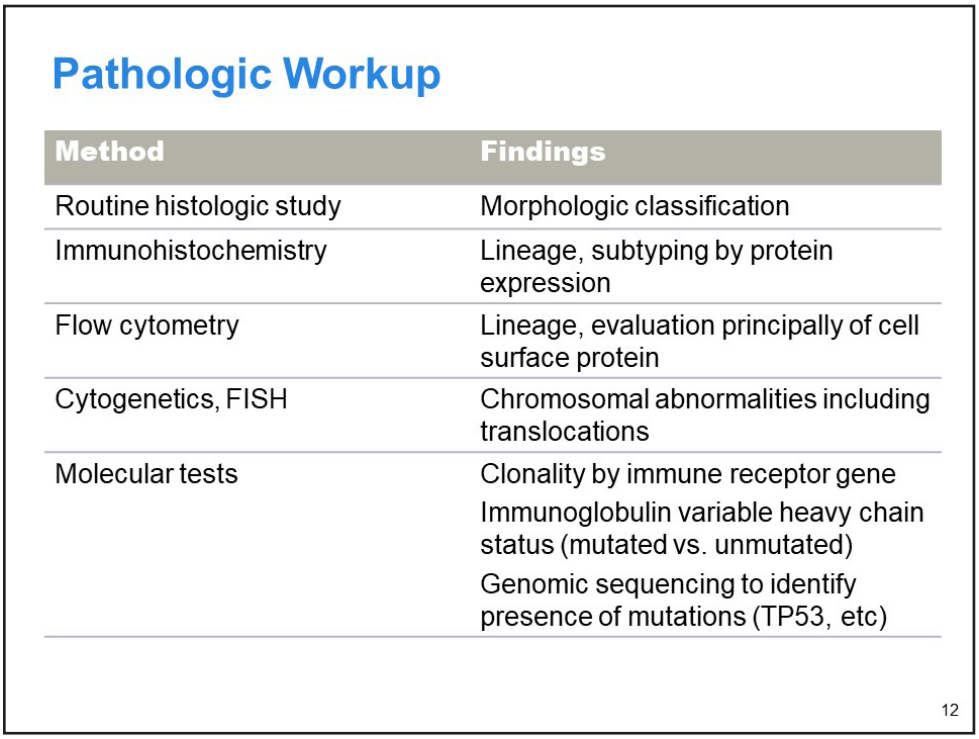
One of the important areas of ongoing research in mantle cell lymphoma is to understand what are the abnormalities at the genetic level that lead to the development of mantle cell lymphoma and how can we better understand the mutations that are present in genes within mantle cell lymphoma cells to develop biologically targeted therapies.



Slide 11: The clinical significance of genetic alterations in MCL is subject of ongoing research

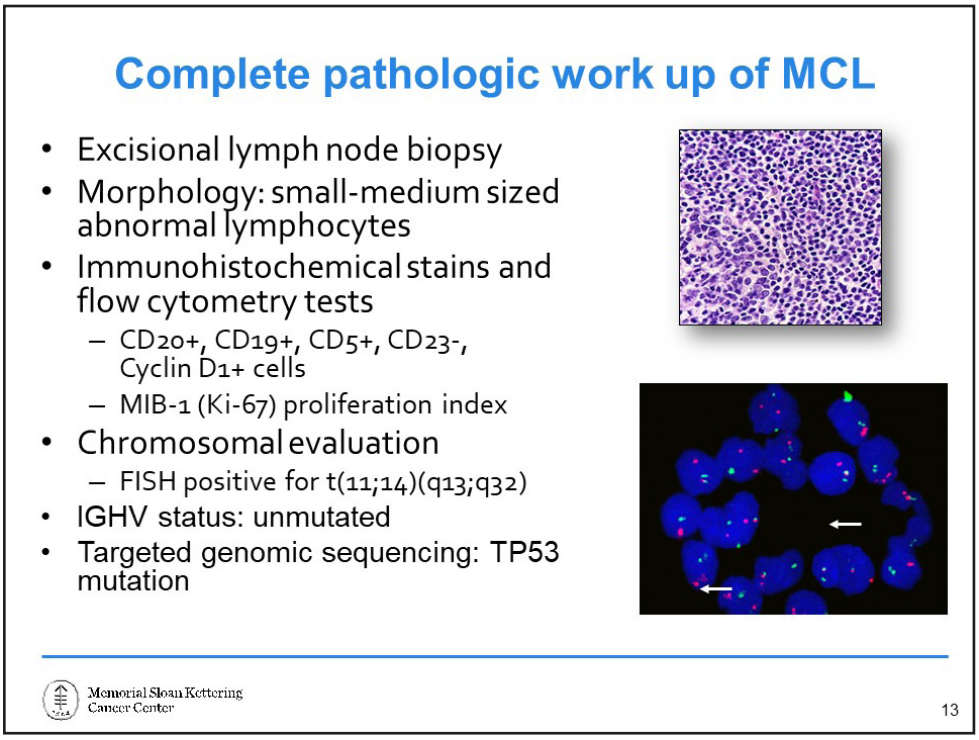
This is some work that has been presented, looking at the common genetic alterations in mantle cell lymphoma. We have been sequencing many of our cases of mantle cell lymphoma at MSKCC, you can see in the panels here on the right-hand side, and we've found that the most common alterations are in genes shown here, ATM, TP53, and others that are important epigenetic modifying genes.

Now, the clinical significance or the prognostic significance of these genetic alterations is not fully understood, however we do know that TP53 alterations or deletions tend to be associated with a less favorable prognosis and tend to be associated with a more aggressive version of mantle cell lymphoma.



Slide 12. Pathologic Workup

Here, I wanted to highlight some of the aspects of a comprehensive pathology workup for mantle cell lymphoma, which I believe is very important for your medical oncologist to best understand your unique mantle cell lymphoma, because we know that not all cases of mantle cell lymphoma are the same. And, the important aspects of a complete pathology workup is, of course, a routine histologic study, which means looking at the slides from a biopsy, like a lymph node biopsy or a bone marrow biopsy, under a microscope, to better characterize the size and the appearance of the cells and the architecture of the collection of the cells. We also look at immunohistochemistry, flow cytometry, specialized genetic testing, such as FISH or cytogenetics, and other molecular tests.



Slide 13. Complete pathologic work up of MCL

I'm going to go to the next slide to show you sort of a characteristic pathology workup for a case of mantle cell lymphoma, the type of workup we would do here at Sloan Kettering to really better understand an individual case of mantle cell lymphoma.

So, oftentimes patients present to us with a swollen lymph node and then this lymph node is surgically resected. This is called an excisional lymph node biopsy.

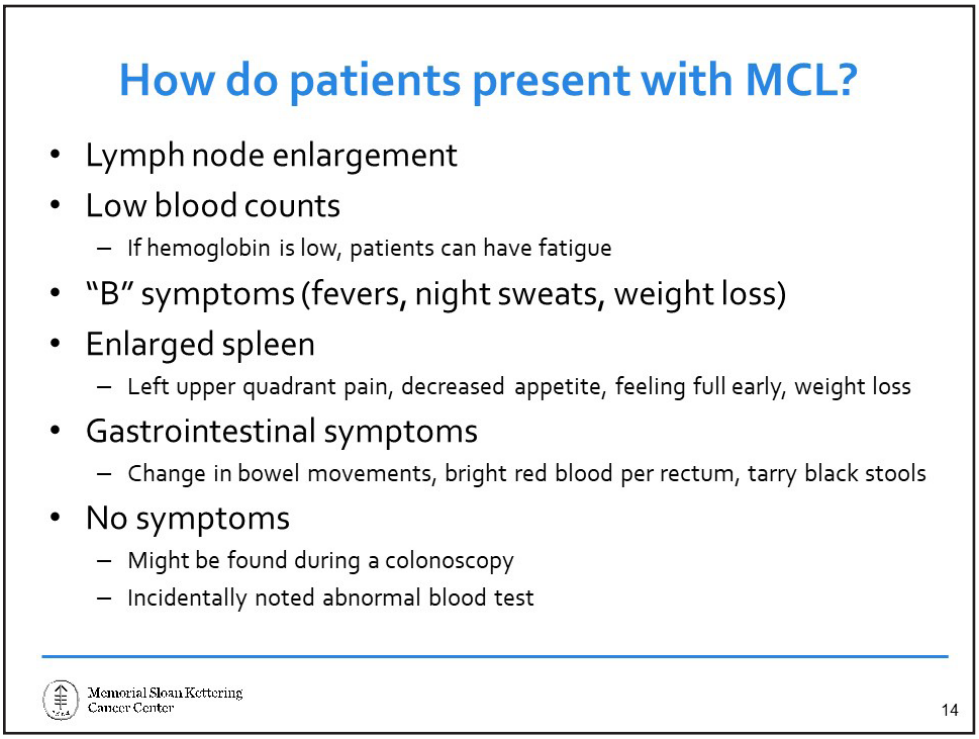
The morphology of a mantle cell lymphoma case is shown here in this H&E slide where we basically see a collection of small- to medium-sized abnormal lymphocytes that are relatively monotonous on this slide.

More specialized stains are done by immunohistochemistry, which allows us to use antibodies to visualize the proteins that are expressed by the cancer cell. There's a characteristic pattern of protein expression associated with mantle cell lymphoma and identification of this characteristic pattern allows us to distinguish mantle cell lymphoma from other subtypes of lymphoma.

The other important immunohistochemistry test is the proliferation index, which on a pathology report may be called Ki-67 or MIB-1. This is an important prognostic indicator, which I'll talk more about later.

There are also specialized genetic tests which we use called FISH testing, which allows us to use a fluorescent probe to assess for changes or rearrangements in the chromosome. And, like I mentioned, the characteristic rearrangement associated with mantle cell lymphoma is a rearrangement between chromosomes 11 and 14.

The other molecular tests that are important is looking at the immunoglobulin heavy chain variable region status, whether it's mutated or unmutated, and, also looking at more sophisticated targeted genomic sequencing that allows us to assess for the presence or absence of TP53 mutation.



Slide 14. How do patients present with MCL?

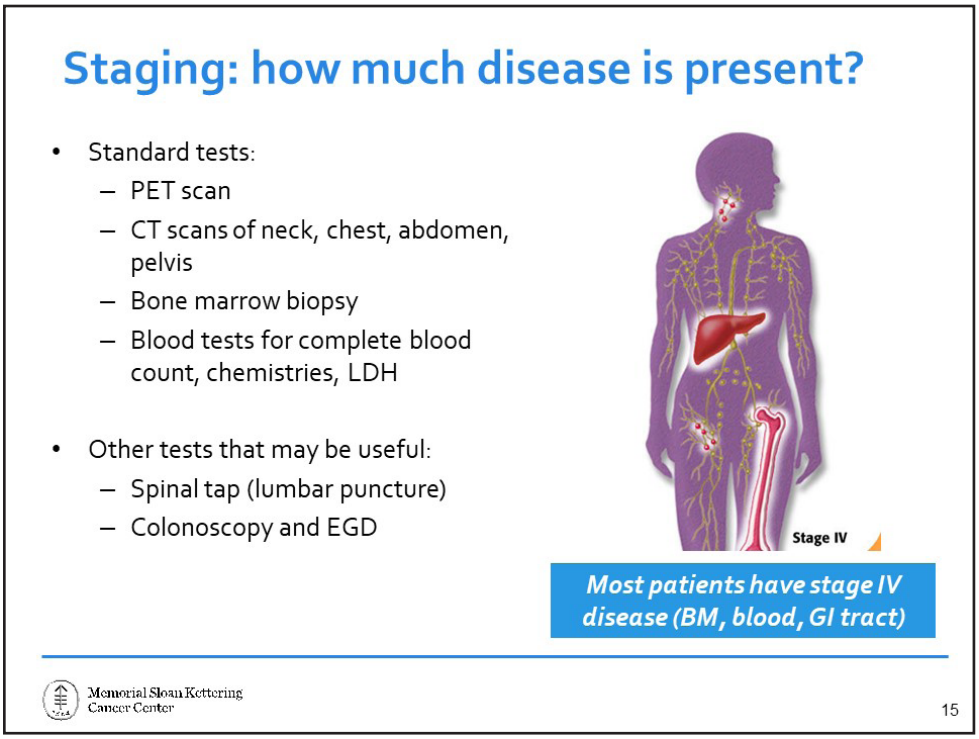
In terms of the common clinical presentation with mantle cell lymphoma, there's many different ways that a patient can present, but, oftentimes a patient will come to medical attention because they notice a new enlargement or swelling in a lymph node.

Other common presenting symptoms or signs are symptoms related to low blood counts. So, if a hemoglobin lowers over time and patients become progressively anemic, they can have fatigue or lightheadedness, shortness of breath when they exert themselves, or palpitations or chest discomfort. Patients can also present with the so-called B symptoms, which are fevers, drenching night sweats, or unexplained weight loss.

Another common presenting symptom with mantle cell lymphoma are symptoms related to an enlarged spleen. The spleen is within the left upper area in the abdomen and as the spleen grows, it can cause discomfort in the left upper quadrant. It can also lead to decreased appetite or a feeling of, after a meal, getting full early because of the way that it can press on the body of the stomach. This can also be associated with significant weight loss.

Mantle cell lymphoma can involve the gastrointestinal tract and patients who have extensive involvement of the GI tract may come to medical attention with bleeding from the GI tract that may present with bright red blood in the toilet bowl or on the toilet paper, or black tarry stools.

And, in some cases, patients may present with mantle cell lymphoma without any particular symptoms, but it may be incidentally found. For example, patients who are undergoing a screening colonoscopy may have biopsies that reveal mantle cell lymphoma, or when they're following up with their general practitioner, it may be noted on blood work that there's abnormalities in terms of an elevated white blood cell count or lymphocyte count or anemia or thrombocytopenia, and then this may initiate further workup that leads to the diagnosis of mantle cell lymphoma.

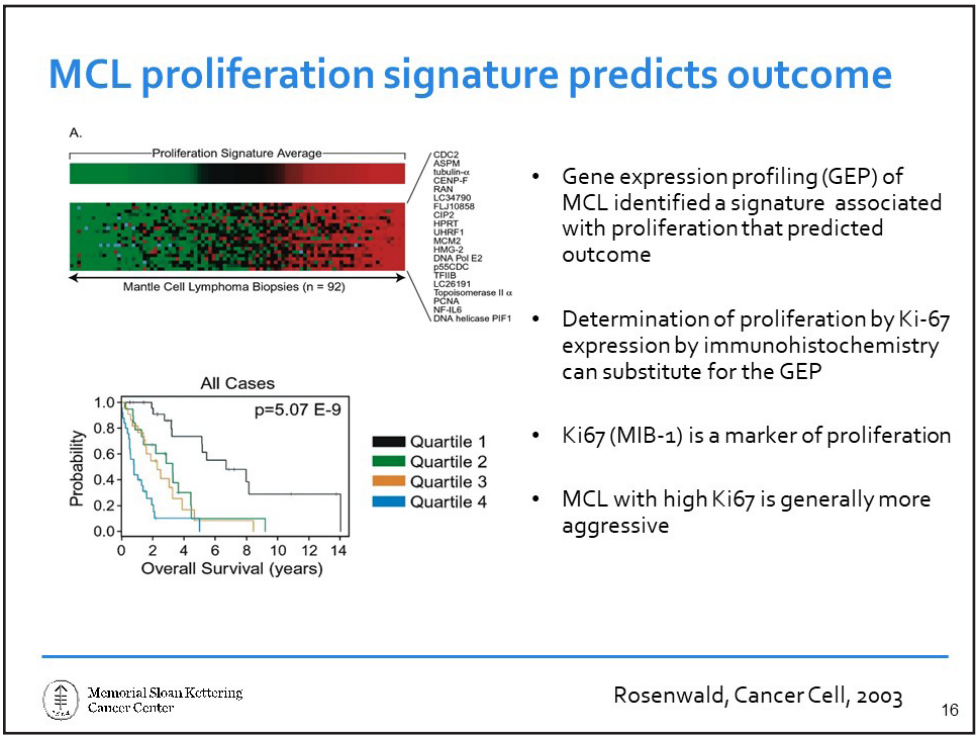


Slide 15. Staging: how much disease is present?

Whenever we have a new patient who presents with lymphoma, the 2 important questions we ask are: one what subtype of lymphoma do they have, and we discuss the pathology workup that's standardly done, and the second question we ask is, how much disease do they have when they initially present? This is an important baseline that we use prior to starting treatment and allows us to be able to stage a patient's mantle cell lymphoma.

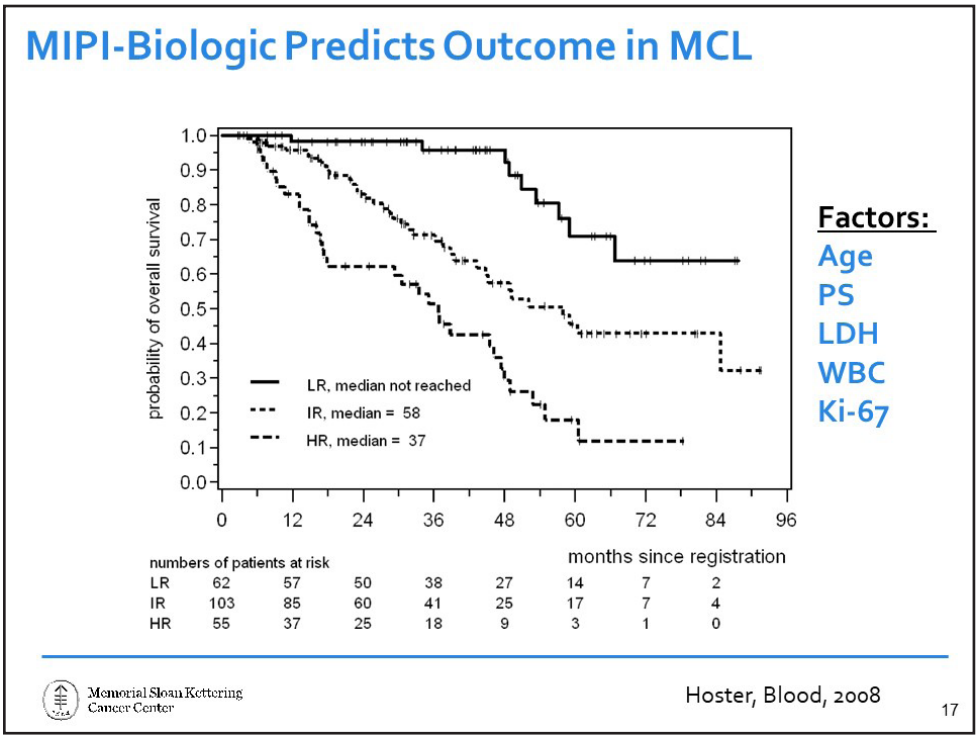
The usual tests that we do for a staging evaluation include a PET scan, a CT scan, a bone marrow biopsy and blood tests, such as a complete blood count, a comprehensive metabolic panel that includes various chemistries and electrolyte levels, as well as an LDH, which is an important prognostic marker.

In some cases, we may perform a spinal tap or a lumbar puncture, or a GI tract evaluation with a colonoscopy and an upper endoscopy, but these are not necessarily indicated in every case.



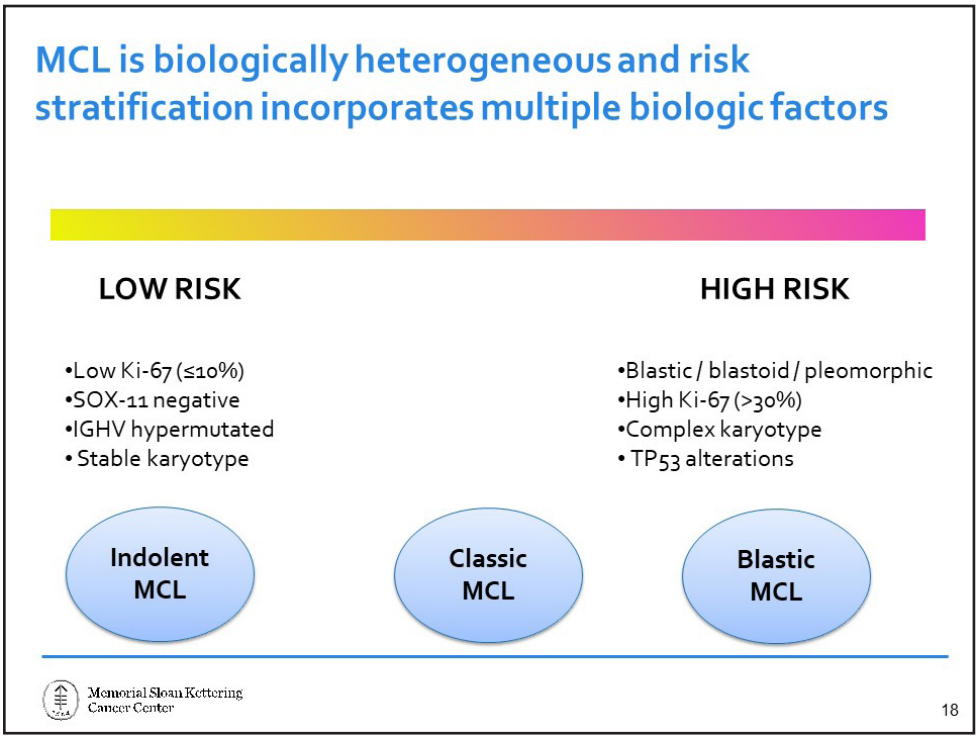
Stage 16. MCL proliferation signature predicts outcome

The mantle cell lymphoma proliferation signature is a pattern of expression of genes that have been identified and associated with outcome in mantle cell lymphoma. This was initially done by more sophisticated gene expression profiling on fresh biopsy specimens for mantle cell lymphoma patients. But now we can use the immunohistochemical test of the Ki-67 or the K-I-67 or MIB-1, as a surrogate marker of proliferation. What has been shown across many different studies is that the Ki-67 is one of the most important prognostic markers in mantle cell lymphoma. And, patients who have a high Ki-67 tend to have more aggressive disease.



Stage 17. MIPI-Biologic Predicts Outcome in MCL

There's different ways of stratifying patients into different risk groups with mantle cell lymphoma. One such tool is called the MIPI-Biologic, which includes the factors shown here: age, performance status, LDH, which is a laboratory test and a marker of tumor burden, white blood cell count, and Ki-67. Putting all these factors together, patients can be separated into different groups as shown here in this graph, which is a curve depicting survival with mantle cell lymphoma. And, what you can see is that the dashed line in the left-hand most curve, this is a high-risk patient who would have – who would meet multiple of these factors and they have an elevated Ki-67, and you can see that this group of patients live less long with the disease as compared to patients who fit into the low-risk group.



Slide 18. MCL is biologically heterogeneous and risk stratification incorporates multiple biologic factors

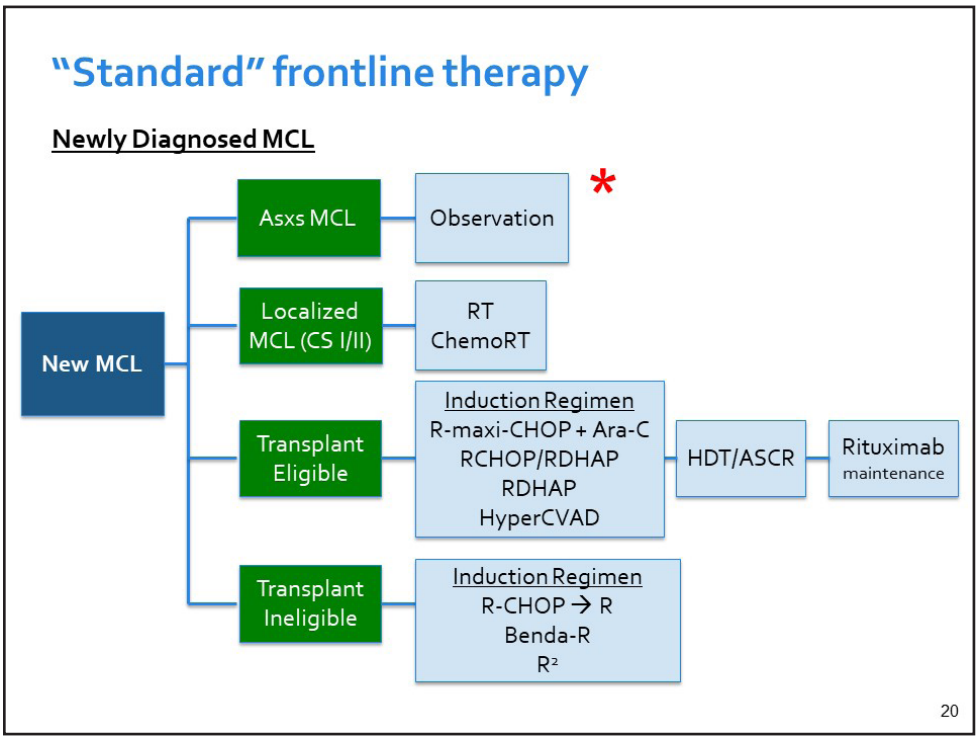
All of this information that I've been mentioning, in terms of the Ki-67 and understanding the presence or absence of particular molecular genetic markers, helps us to stratify patients into different risk groups. And, what we understand now is that there's a subset of patients who have low-risk mantle cell lymphoma, which means their disease grows more slowly. And, many of these patients may be candidates for initial observation or expectant monitoring with indolent mantle cell lymphoma. The characteristics that go along with indolent mantle cell lymphoma are a low proliferation rate or low Ki-67, less than or equal to 10%; the absence of a transcription factor called SOX-11; hypermutated immunoglobulin heavy chain variable region; and a stable karyotype, which means very few chromosomal abnormalities beyond the characteristic chromosomal abnormality that we discussed between chromosomes 11 and 14.

In contrast, high-risk patients will have features of what's called blastic, blastoid, or pleomorphic mantle cell lymphoma. This is a description of how the mantle cell lymphoma cells look under the microscope. We talked about how usually mantle cell lymphoma atypical lymphocytes are small or medium size, but patients who have blastic or blastoid mantle cell tend to have larger cells that are dividing more rapidly. Oftentimes, these cases will also be associated with an elevated Ki-67 or proliferation index, they may have multiple chromosomal abnormalities, and potentially an abnormality in the TP53 gene.

The reality is, is that a small proportion of patients fit into either the low or the high-risk group with mantle cell lymphoma. Most patients actually have classic mantle cell lymphoma and we're trying to better understand the differences between these patients, about 85% of patients with classic mantle lymphoma, in terms of their disease biology, so that we can better select biologically targeted therapies based on somebody's initial presentation.

Slide 19. Emerging therapies for MCL

So, with this, I'll move to the emerging therapies for mantle cell lymphoma.



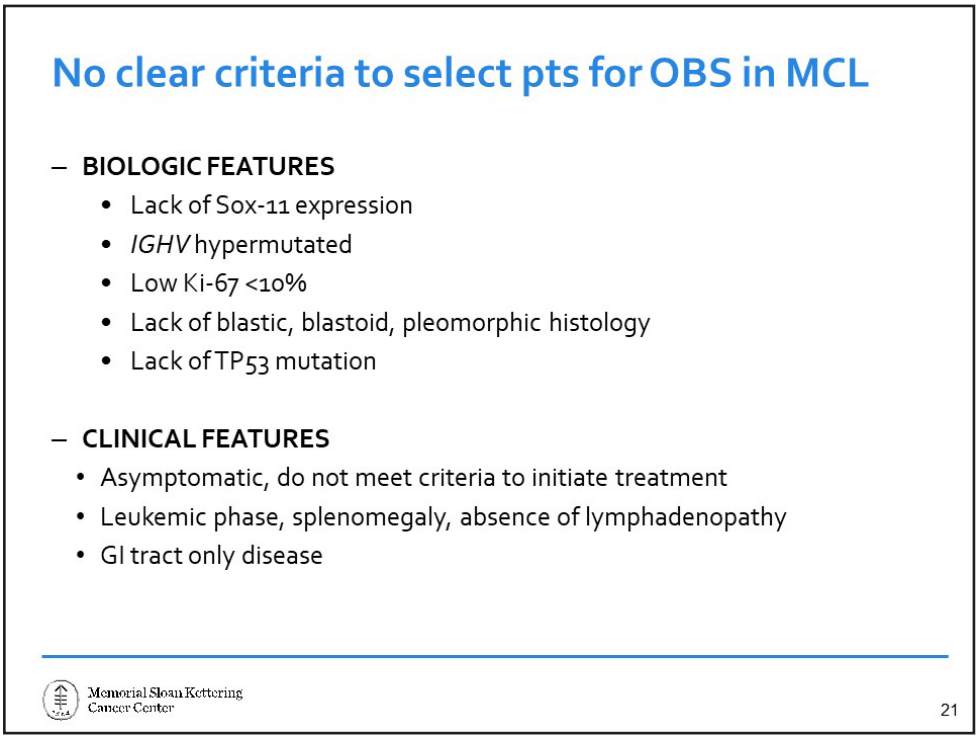
Slide 20. "Standard" frontline therapy

Because mantle cell lymphoma is a rare disease, we actually do not have the ability to do, in most cases, large randomized trials to establish a standard approach for mantle cell lymphoma. The other reason why it's difficult to define a standard approach for mantle cell lymphoma relates to what I was describing before, that not all mantle cell lymphoma patients are the same, and because of the biologic heterogeneity, there's not a one-size-fits-all approach. So, in this slide I put quotation marks around standard because I don't believe there's necessarily one standard of care. And, actually for a patient

even with newly diagnosed mantle cell lymphoma, enrollment in a clinical trial with access to novel therapies is a very appropriate approach for this type of disease.

So, using the information that we talked about before, when I meet a new patient with mantle cell lymphoma, I typically put them into 1 of these 4 different categories when thinking about what is the best initial approach to treatment.

The first category is a patient who presents with mantle cell lymphoma, who is asymptomatic and has a low tumor burden. These types of patients, oftentimes have the favorable biologic features that I discussed, like a low proliferation rate, and are potential candidates for observation.



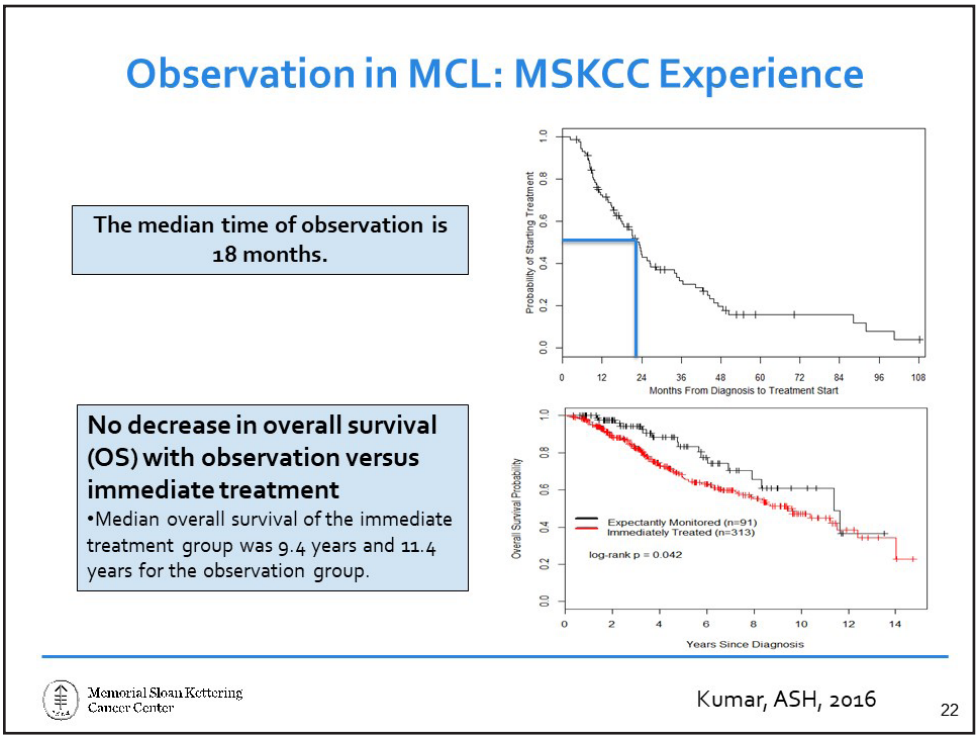
Slide 21. No clear criteria to select pts for OBS in MCL

There are no clear criteria to select patients for expectant monitoring or observation in mantle cell lymphoma, but some of the things that could lead a medical oncologist to decide that observation was an appropriate strategy for a patient, would include the presence of certain biologic features, as well as certain clinical features. So, we discussed the biologic features that are associated with indolent mantle cell lymphoma. In terms of the clinical features, oftentimes these patients come to medical attention without significant symptoms. For example, they don't have recurrent fevers or drenching night sweats. They're overall feeling well.

Oftentimes, they will present with a characteristic pattern of involvement with their disease, which involves leukemic phase or involvement within the blood, an enlarged spleen, and an absence of enlarged lymph nodes. This leukemic phase mantle cell lymphoma is oftentimes associated with more indolent disease, and these patients are oftentimes very good candidates for observation.

In some cases, these patients are actually misdiagnosed initially with CLL or chronic lymphocytic leukemia because they may have just an elevated – an incidentally noted elevated white blood cell count. And, oftentimes these patients can be seen in clinic every 3 to 6 months and can be monitored for any disease progression over time.

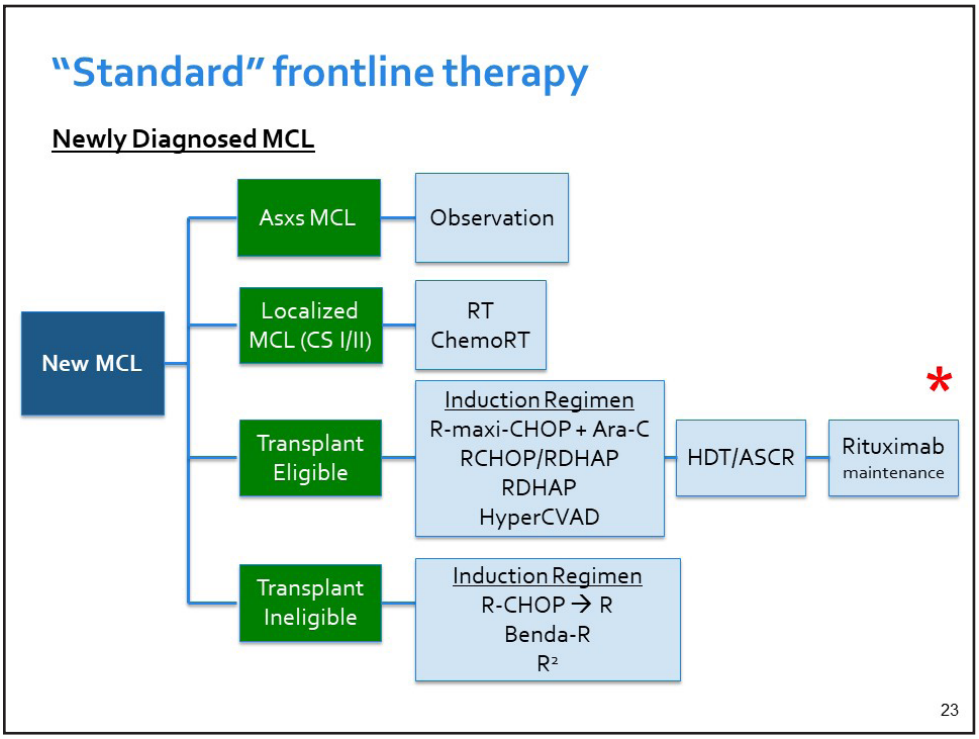
The other category of patients who are often good candidates for observation are people who have incidentally noted mantle cell lymphoma when they do a screening colonoscopy and they only have involvement of their gastrointestinal tract, and when you do a PET scan and a bone marrow biopsy and other workup, they have no other evidence of disease. There's about 10 to 15% of mantle cell lymphoma patients who fit into this category of disease.



Slide 22. Observation in MCL: MSKCC Experience

We have looked specifically at this group of patients at Memorial Sloan Kettering and we identified from 2000 to 2012, 90 patients who were expectantly monitored with mantle cell lymphoma. And, what we found was that patients who were selected for initial observation were followed for an average time of 18 months or median time of 18 months. And, we found that there was no decrease in the overall survival associated with an initial selection to observe a patient versus immediate treatment. And, these findings have also been published in multiple other centers, such as Cornell, New York Presbyterian and at Emory, where they've published very similar results that observation is a reasonable strategy for patients with indolent mantle cell lymphoma.

Now, there is another subgroup of patients who can present with localized mantle cell lymphoma. This is very rare. And, these patients can potentially be candidates for radiation or chemo plus radiation.

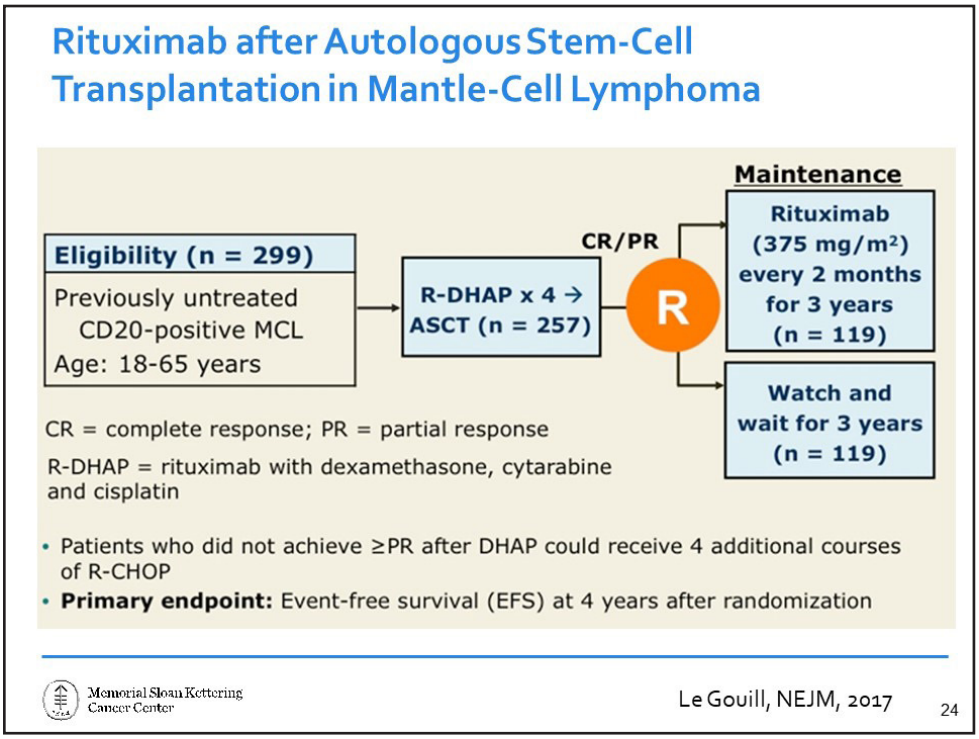


Slide 23. "Standard" frontline therapy

I'll move on, though, to the grand majority of patients who present with symptoms related to their lymphoma and more significant lymphoma involvement in terms of lymph nodes and other sites of disease. Most of these patients require initial or immediate initiation of chemotherapy, and there's different approaches. Historically, we have split people into 2 groups: those that are younger and transplant-eligible versus those that are older and transplant-ineligible.

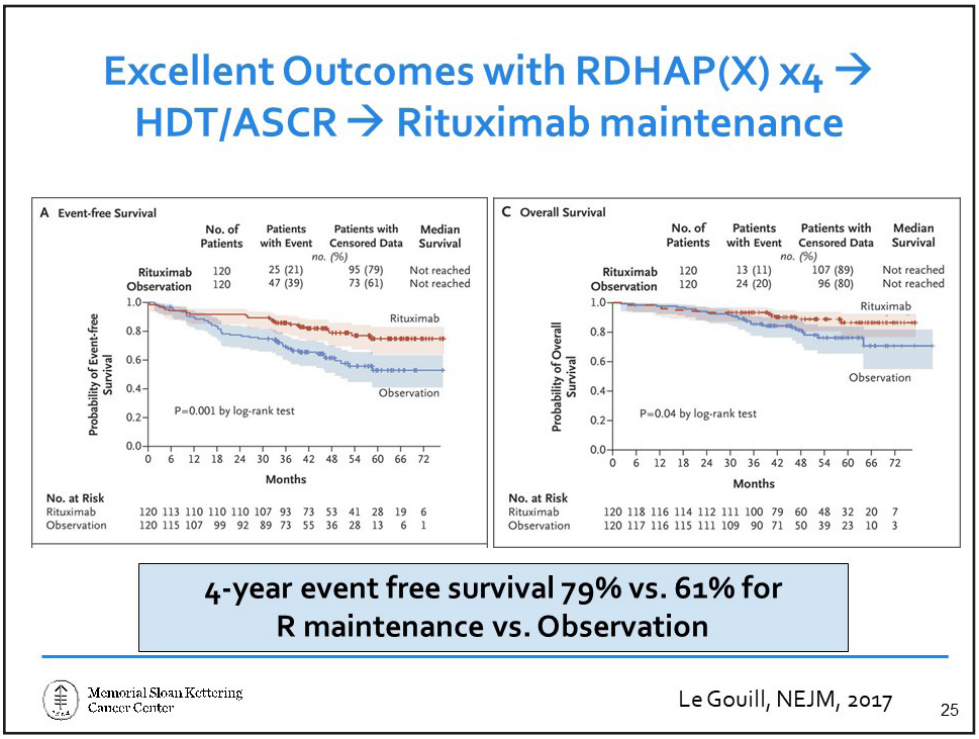
When we are talking about transplant here, we're talking about an autologous stem cell transplant, which uses stem cells from an individual person as a consolidation after completion of initial chemotherapy.

So, for young fit patients, a very reasonable approach is to receive initial induction chemotherapy followed by high-dose therapy and autologous stem cell transplant, followed by rituximab maintenance.



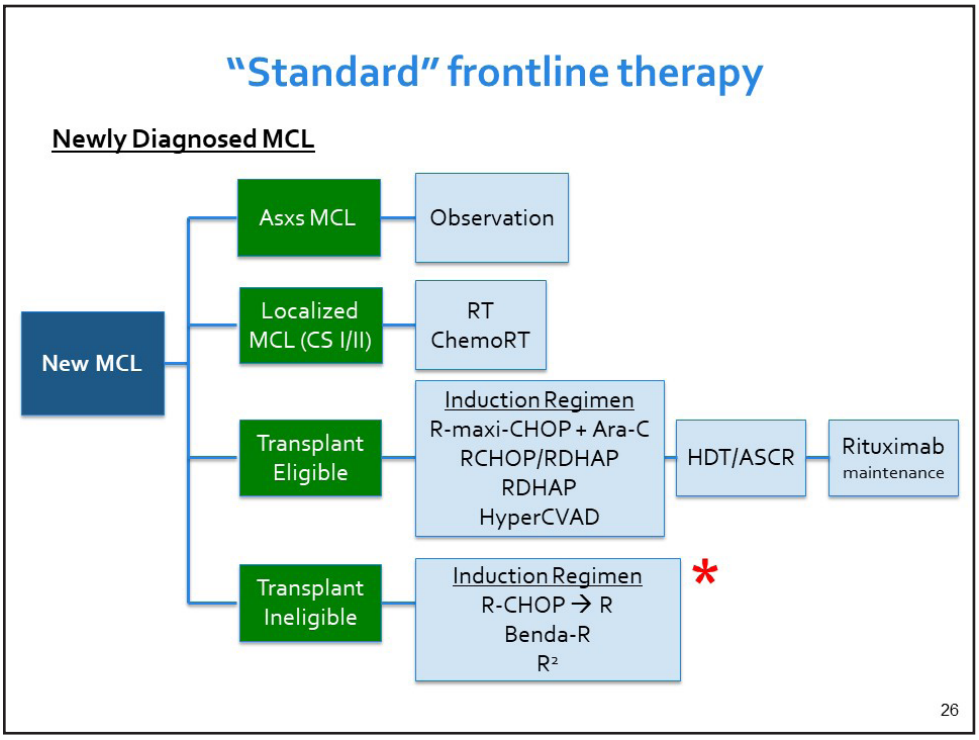
Slide 24. Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma

This approach was recently published in the *New England Journal of Medicine* in 2017. This was a study that was performed in Europe and patients who were younger, so 18 to 65 years of age, who presented with previously untreated mantle cell lymphoma, were enrolled in this randomized study, where patients initially received rituximab, which is a monoclonal antibody against CD20, in combination with a chemotherapy program called DHAP. They received 4 cycles of this treatment. If they were sensitive to this chemotherapy and achieved a complete or partial response, they were then randomized to either receive rituximab maintenance or to be observed.



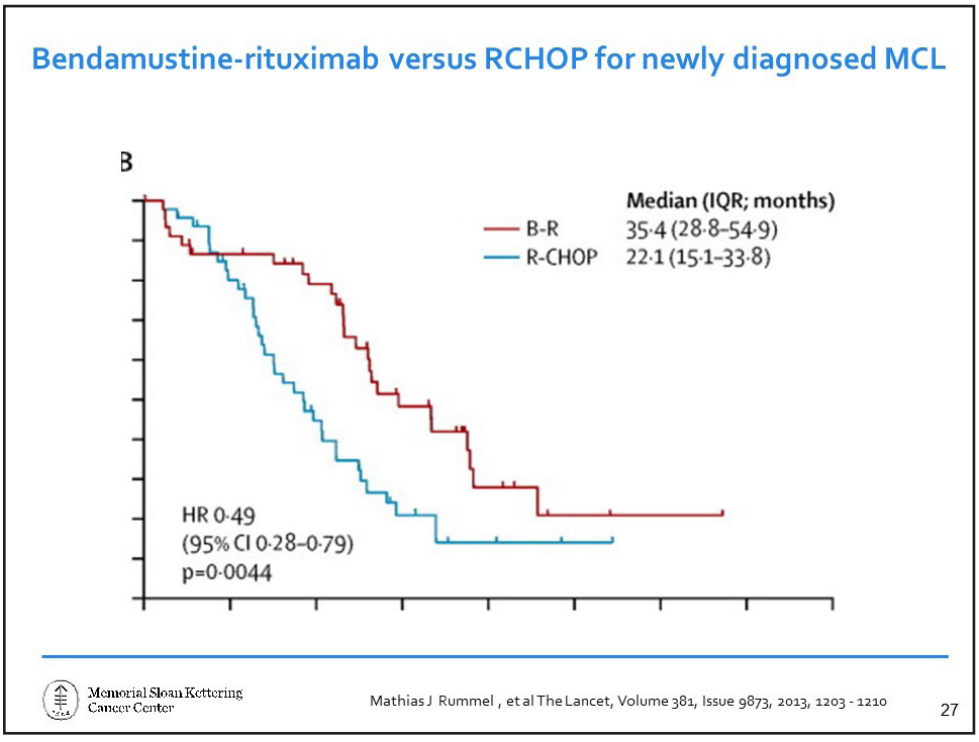
Slide 25. Excellent Outcomes with RDHAP(X) x4 → HDT/ASCR → Rituximab maintenance

This study looked at the event-free survival after 4 years after the randomization point, and compared the 2 arms. What they found was that there was a significant improvement in progression-free survival or event-free survival and overall survival with rituximab maintenance that was administered after an autologous stem cell transplant. And, so here you can see that the red curve is significantly above the blue curve in both of these graphs, for event-free survival and overall survival. And, because of this data, we are now recommending for any patients who undergo initial induction chemotherapy followed by stem cell transplant, that they then receive afterward rituximab maintenance, which is typically given every 2 months for a total of 3 years, because there was a significant improvement in event-free and overall survival with this approach.



Slide 26. "Standard" frontline therapy

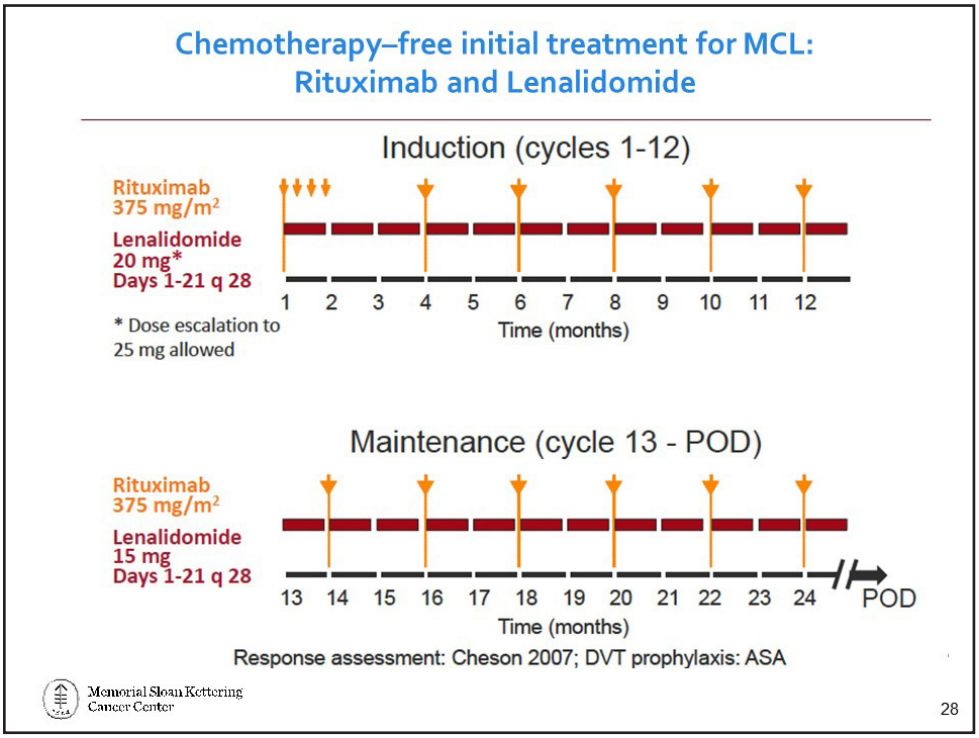
For patients who are older or who have other medical issues which make them transplant-ineligible, we use different chemotherapy regimens, which are better tolerated and less toxic than the high-dose therapy and autologous stem cell approach that I just discussed.



Slide 27. Bendamustine-rituximab versus RCHOP for newly diagnosed MCL

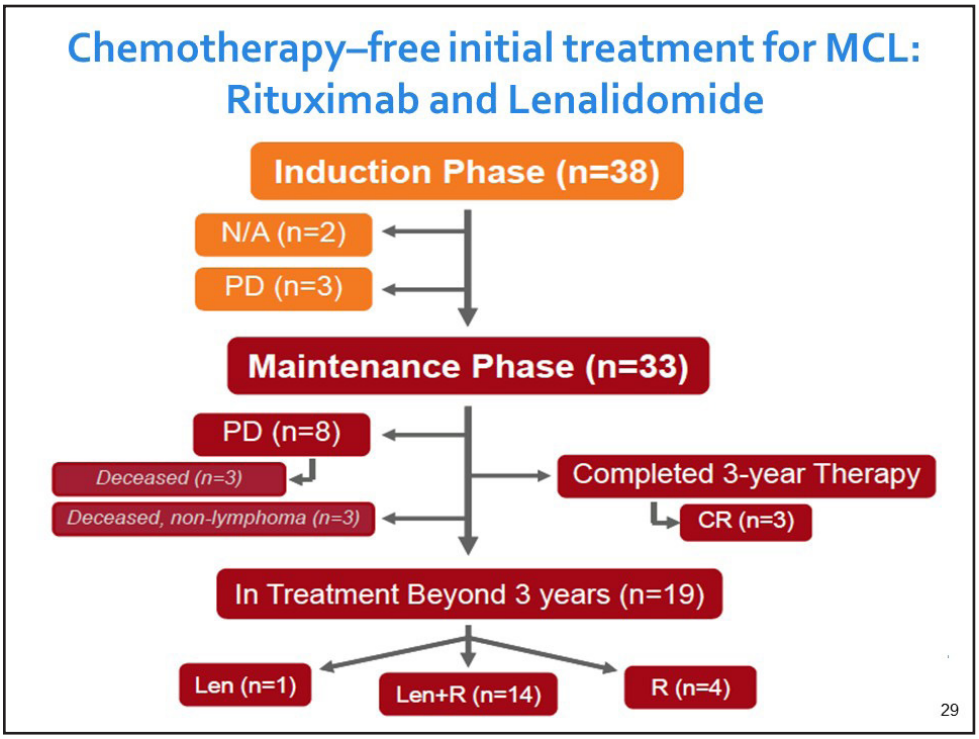
One of the most effective treatments for patients who are older or have other medical issues that prevent receipt of a transplant, is a regimen that is called bendamustine and rituximab (BR). Bendamustine and rituximab were compared to R-CHOP chemotherapy, which used to be the standard of care for mantle cell lymphoma, and was found to be superior

in terms of progression-free survival. And, so patients who receive bendamustine and rituximab in general, tolerate the treatment much better than patients with R-CHOP, there's fewer side effects, and also seem to have better outcomes in mantle cell lymphoma.



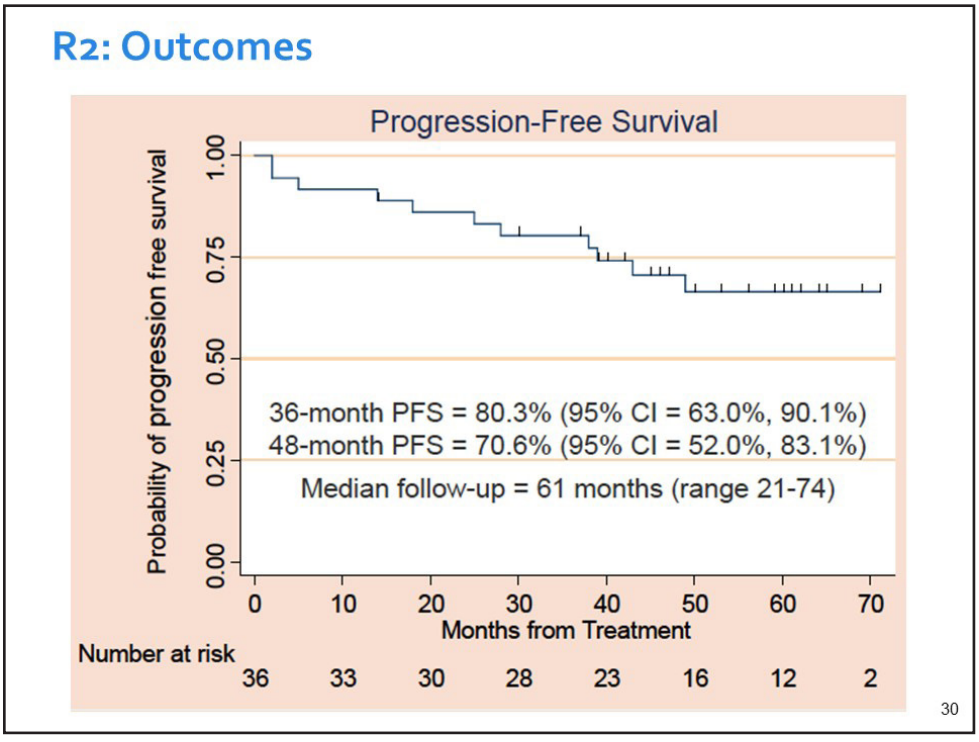
Slide 28. Chemotherapy–free initial treatment for MCL: Rituximab and Lenalidomide

Another very interesting study that was recently presented at this year's American Society of Hematology (ASH) conference was a study published by Dr. Jia Ruan and published in the New England Journal of Medicine, which is a chemotherapy-free initial treatment for mantle cell lymphoma, which includes rituximab and an immune modulatory drug called lenalidomide. This was given initially for 12 cycles, monthly cycles, at a dose of lenalidomide 20 milligrams in combination with rituximab, and then given in maintenance at a slightly lower dose of lenalidomide. Patients were continued on treatment until they progressed.



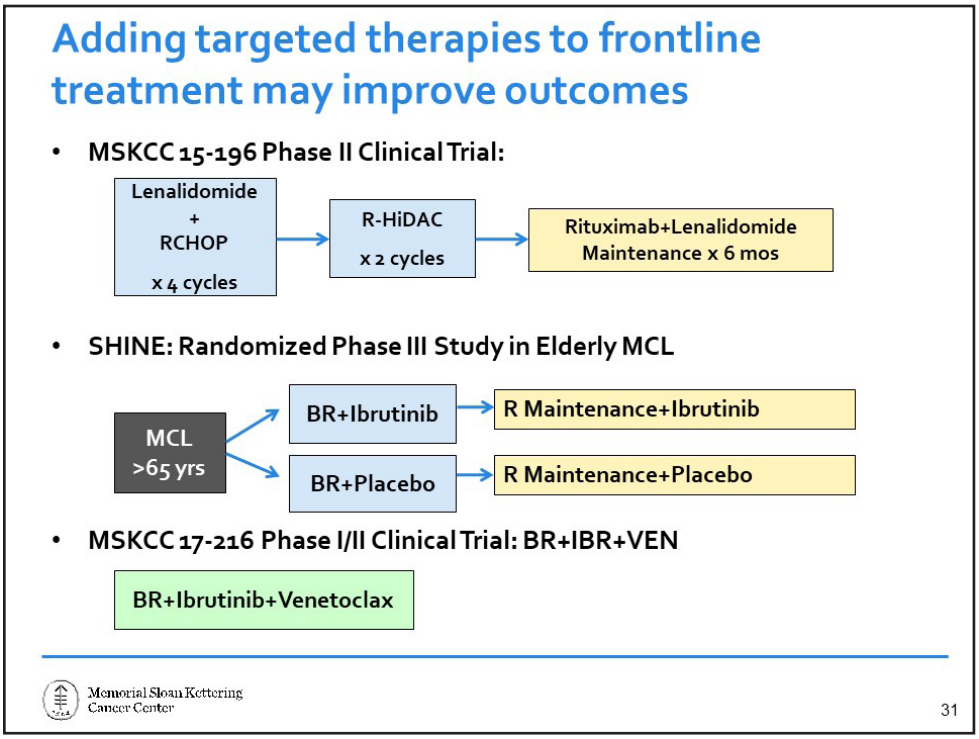
Slide 29. Chemotherapy–free initial treatment for MCL: Rituximab and Lenalidomide

This was a small study with 38 patients who were included, and 33 of the 38 were able to get to the maintenance phase of treatment. And, what Dr. Ruan presented was that there was a significant proportion, 19 patients of the 33, who were still receiving lenalidomide and rituximab beyond 3 years, and achieved excellent outcome with this chemotherapy-free approach.



Slide 30. R_2: Outcomes

And, so you can see here that the 48-month progression-free survival is around 70%, which basically means that at 4 years after treatment, 70% of patients were continuing in remission. And, so this is also a very nice treatment option potentially for patients who cannot tolerate intensive chemotherapy.



Slide 31. Adding targeted therapies to frontline treatment may improve outcomes

There are a number of new approaches that are being studied for the frontline treatment of mantle cell lymphoma. The clinical trial that we have open for the frontline treatment of mantle cell lymphoma patients is a Phase II clinical trial in which we're using a standard chemotherapy regimen and adding to it lenalidomide, which is the immune modulatory drug, that has substantial activity in mantle cell lymphoma. There are 3 phases of treatment on our trial, it's lenalidomide plus R-CHOP, followed by rituximab and high-dose cytarabine, which is a treatment that's given in the hospital for a few days, and then instead of doing a stem cell transplant, instead we're giving rituximab and lenalidomide maintenance.

The reason for that is because increasingly there's more and more evidence that maintenance is a very effective treatment that can be utilized for consolidation to essentially mop up any residual mantle cell lymphoma cells, and may be just as effective as an autologous stem cell transplant, but significantly less toxic, not requiring a month in the hospital and close follow-up for several months afterward.

And, what we've seen so far with this clinical trial is that it's a very effective treatment program and, you know, we're looking forward to analyzing the final results of this study.

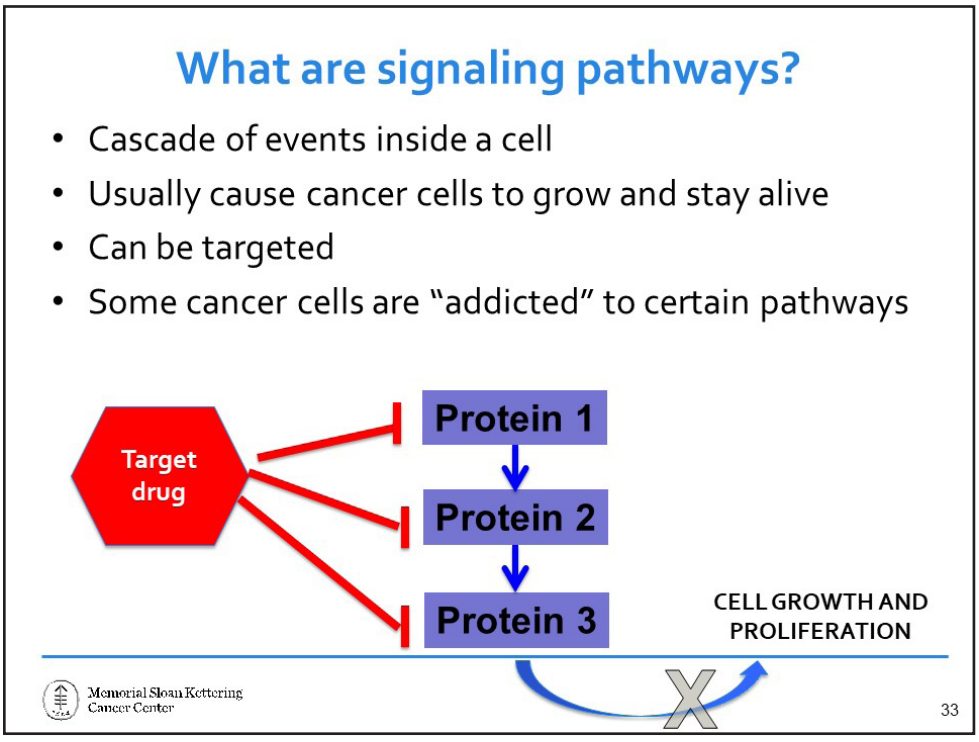
The other important frontline study in mantle cell lymphoma that I will highlight is the SHINE study, which has fully accrued patients and now we're just waiting for the final results of the trial to come out. What this study looked at was using bendamustine and rituximab, which is the highly effective and well-tolerated treatment program that we use typically for patients who are not transplant-eligible. BR was the chemotherapy platform in the study and patients were randomized to either receive BR plus ibrutinib, which is a novel therapy that I'll talk a little bit more about, and it's also called Imbruvica®, or to receive BR without any additional treatment. And, after completing initial chemotherapy for 6 cycles, patients receive maintenance with rituximab and ibrutinib for the investigational arm, and with placebo for the control arm. And, so we're eagerly awaiting this study to see whether the addition of ibrutinib to BR will improve outcomes. And, hopefully in the next 1 to 2 years we'll see the results of that study come to the forefront.

And, another trial that we're excited about here at MSKCC, that has opened, is a Phase I/II study looking at BR plus ibrutinib plus another very exciting drug in mantle cell lymphoma called venetoclax, which is a BCL2 inhibitor. This is a study that we are eager to see if it could potentially represent an improvement beyond BR and ibrutinib. If the SHINE results end up being positive, this could be the next potential frontline regimen that could be even more effective in the future.

So, the concept here is really to add the new treatments, lenalidomide, ibrutinib, and venetoclax, to some of the standard chemotherapy platforms to see if we can get even better remission rates and improve the outcomes for patients with mantle cell lymphoma.

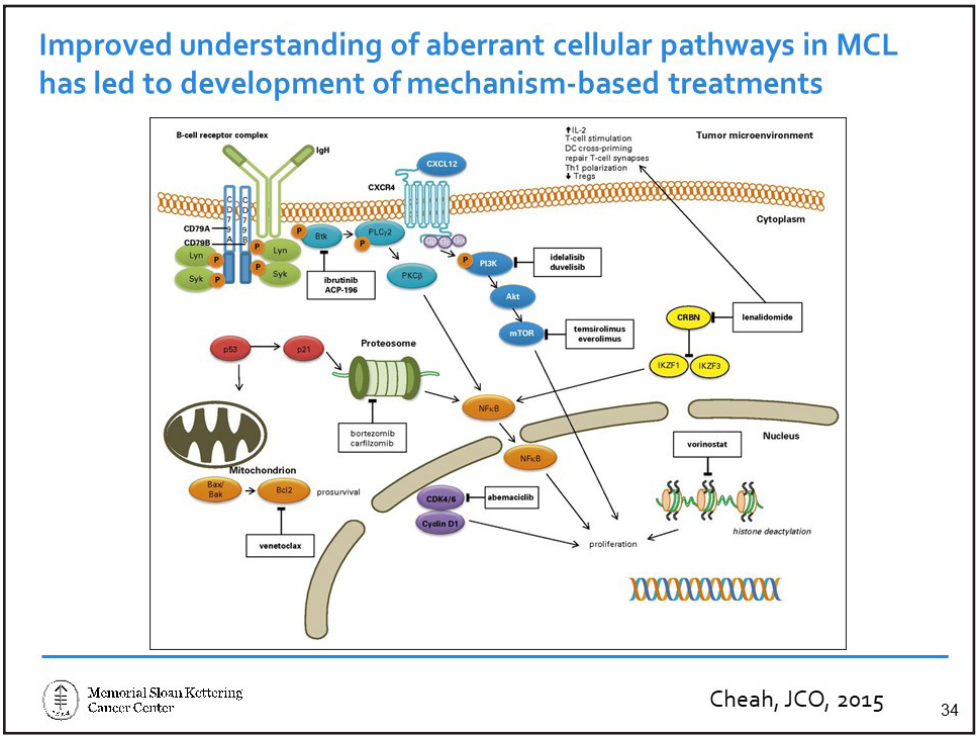
Slide 32. WHEN MCL COMES BACK (also called recurrent or relapsed disease)

So, I'd like to talk a little bit about how we approach the treatment of mantle cell lymphoma when it comes back after initial treatment.



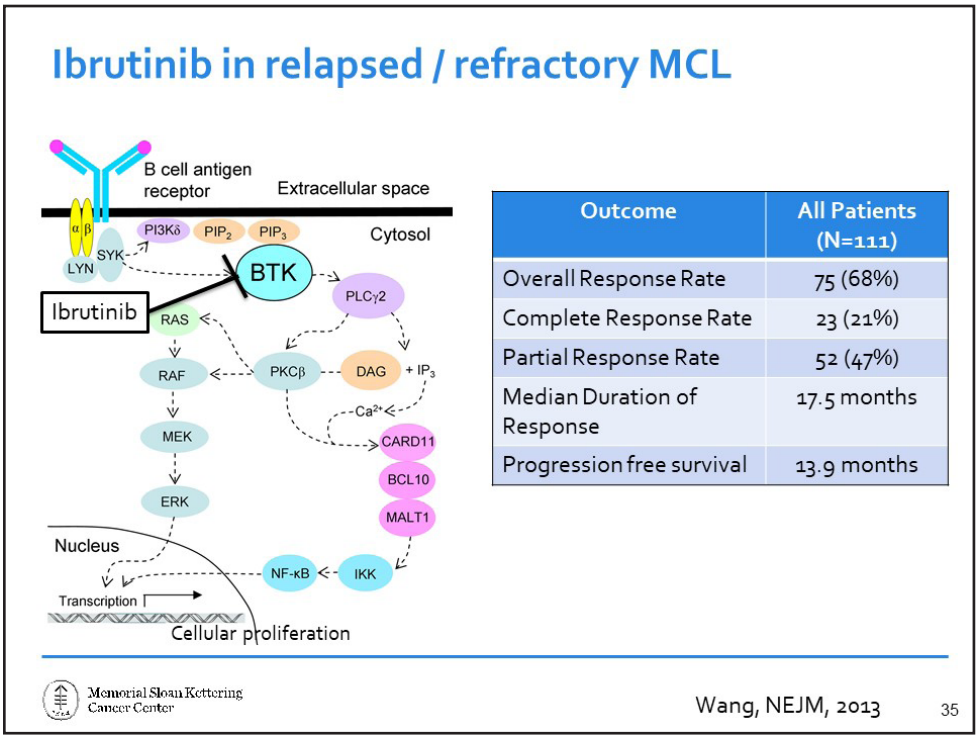
Slide 33. What are signaling pathways?

I'm going to just skip this slide in the interest of time.



Slide 34. Improved understanding of aberrant cellular pathways in MCL has led to development of mechanism-based treatments

But, basically what we are trying to do is to better understand the abnormal pathways within the cell that drive cells to grow and divide with mantle cell lymphoma. And, better understanding these different pathways like the B cell receptor pathway, the NF kappa B pathway, the PI3 kinase pathway, all of these different pathways are important pathways that can be targeted with biologically targeted therapies, to block the signal that's being passed along, and to halt the growth of the cell and to more effectively kill and treat mantle cell lymphoma.

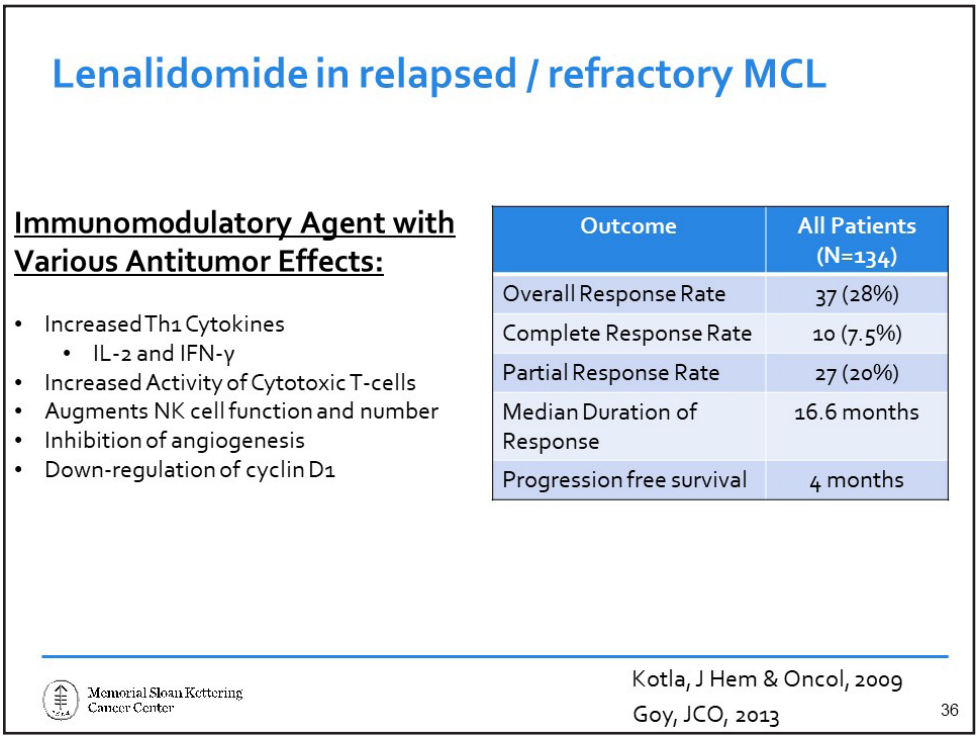


Outcome	All Patients (N=111)
Overall Response Rate	75 (68%)
Complete Response Rate	23 (21%)
Partial Response Rate	52 (47%)
Median Duration of Response	17.5 months
Progression free survival	13.9 months

Slide 35. Ibrutinib in relapsed / refractory MCL

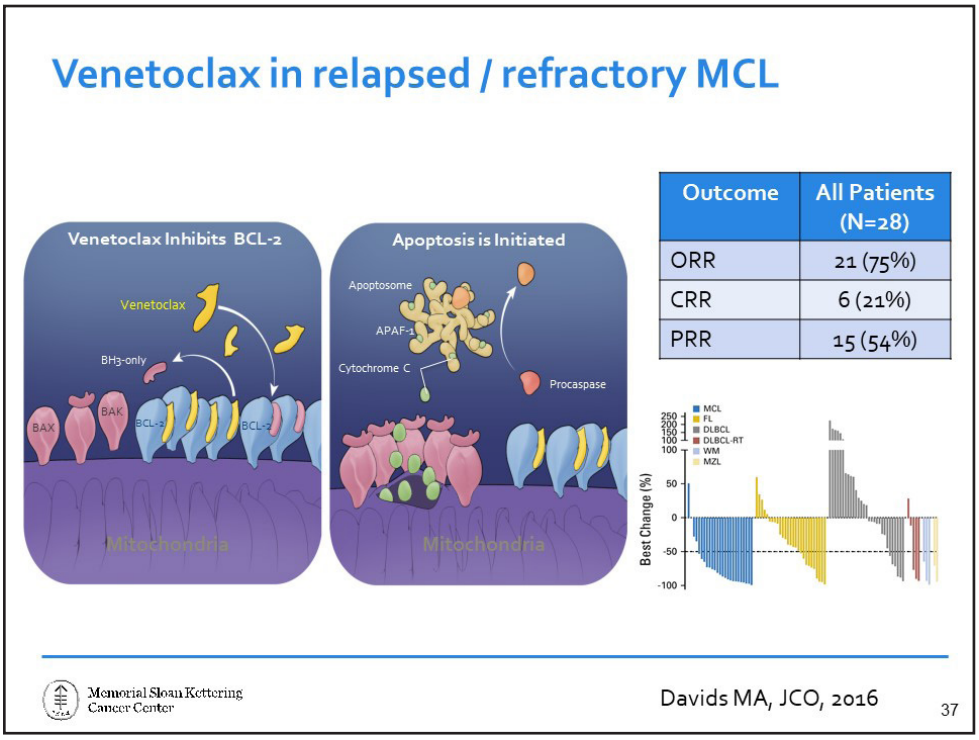
One of the most effective treatments for relapsed/refractory mantle cell lymphoma is ibrutinib or Imbruvica. This treatment involves an oral drug which is taken daily and the ibrutinib blocks a protein called Bruton's tyrosine kinase, which is an important protein within the B cell receptor pathway, which we know is turned on in mantle cell lymphoma and leads to increased proliferation of cells. The data from the initial study that led to the FDA approval of ibrutinib showed an overall response rate of around 70% and a complete response rate of around 20%.

Unfortunately, what we see is that the median duration of response for all-comers with ibrutinib is only 18 months and the progression-free survival 14 months, meaning that there's only a proportion of patients who are able to stay on ibrutinib for a long period of time, and in most patients, this gives a remission duration of only about a year or a year and a half, and we'd like that to be much longer.



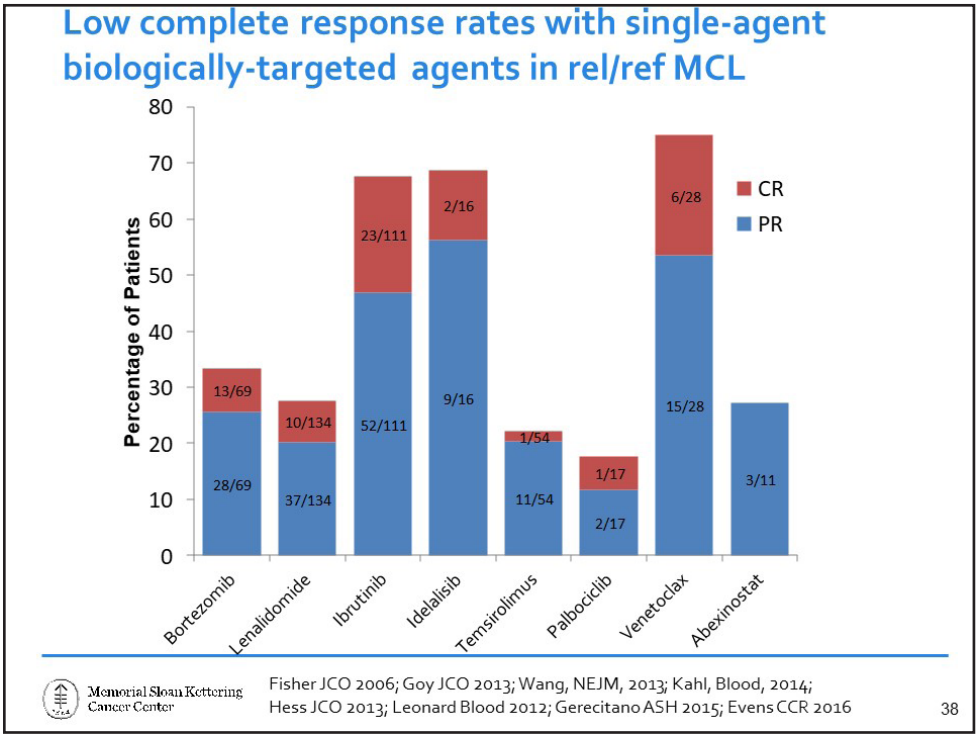
Slide 36. Lenalidomide in relapsed / refractory MCL

Lenalidomide, as we talked about, is an immune modulatory drug. It has a variety of different effects on immune cells in the microenvironment around the mantle cell lymphoma cells, and it helps to stimulate the immune response against the tumor cells. This has been shown to be associated with an overall response rate of around 28% and, unfortunately, a low complete response rate of only 7.5% in the relapsed/refractory population, and the duration of response is short as well.



Slide 37. Venetoclax in relapsed / refractory MCL

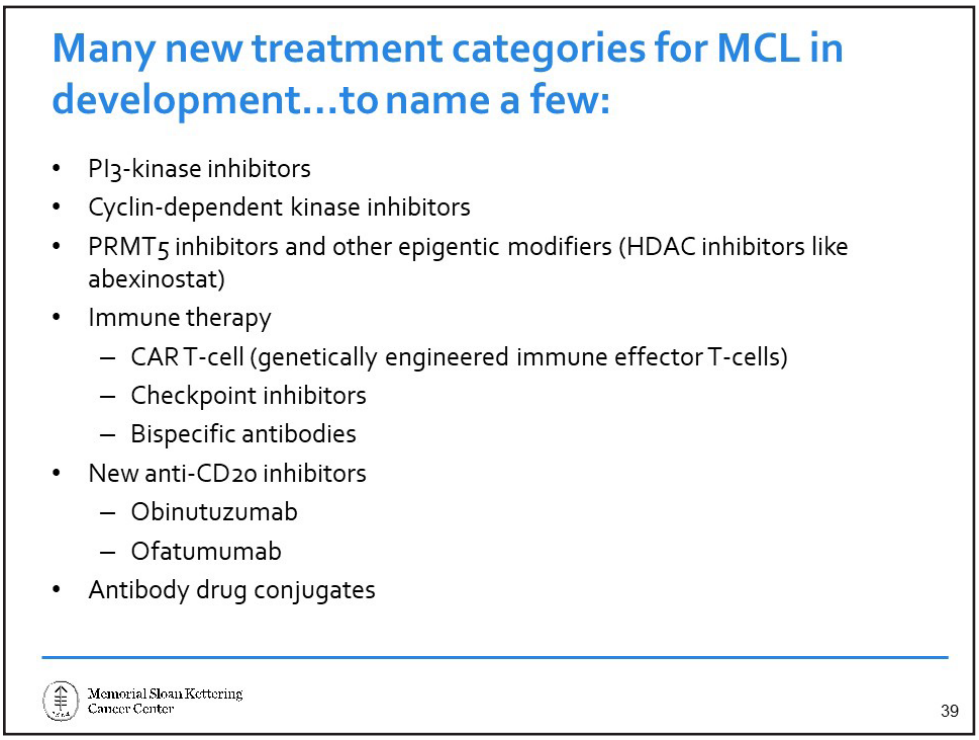
Venetoclax, which is not FDA approved for the treatment of mantle cell lymphoma yet, but is part of the NCCN (National Comprehensive Cancer Network) guidelines for the treatment of relapsed/refractory mantle cell lymphoma, is a drug that inhibits the protein BCL2, which is an important protein within the programmed cell death pathway or the apoptotic pathway. And, it pushes cells towards apoptosis or cell death. This has been shown to be associated with an impressive overall response rate of 75% and a complete response rate of around 21%.



Slide 38. Low complete response rates with single-agent biologically-targeted agents in rel/ref MCL

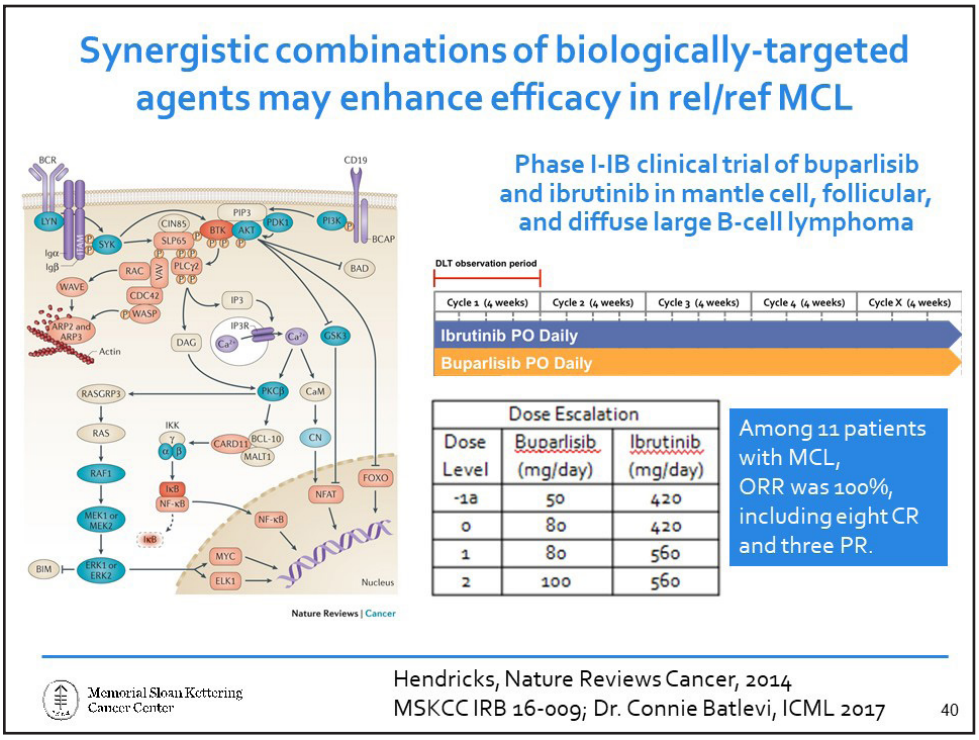
This is a slide that summarizes the response rates for different biologically targeted drugs in the relapsed/refractory setting for mantle cell lymphoma.

We are really truly excited that there is more and more different categories of drugs that are active in mantle cell lymphoma, such as bortezomib, which is a proteasome inhibitor, lenalidomide, ibrutinib, as we talked about. Idelalisib is a PI3 kinase inhibitor. Temsirolimus is an mTOR inhibitor. This drug is a CDK46 inhibitor, which is shown to be effective. And, this is an HDAC inhibitor. All of these different new categories of drugs have activity in mantle cell lymphoma. However, you can see by the red here that the degree to which these drugs can result in a complete remission versus a partial remission, complete remission is when you see no evidence of the disease after putting somebody on treatment and when you repeat a PET scan nothing lights up, consistent with active lymphoma. The CR rate is lower than what we would like to see.



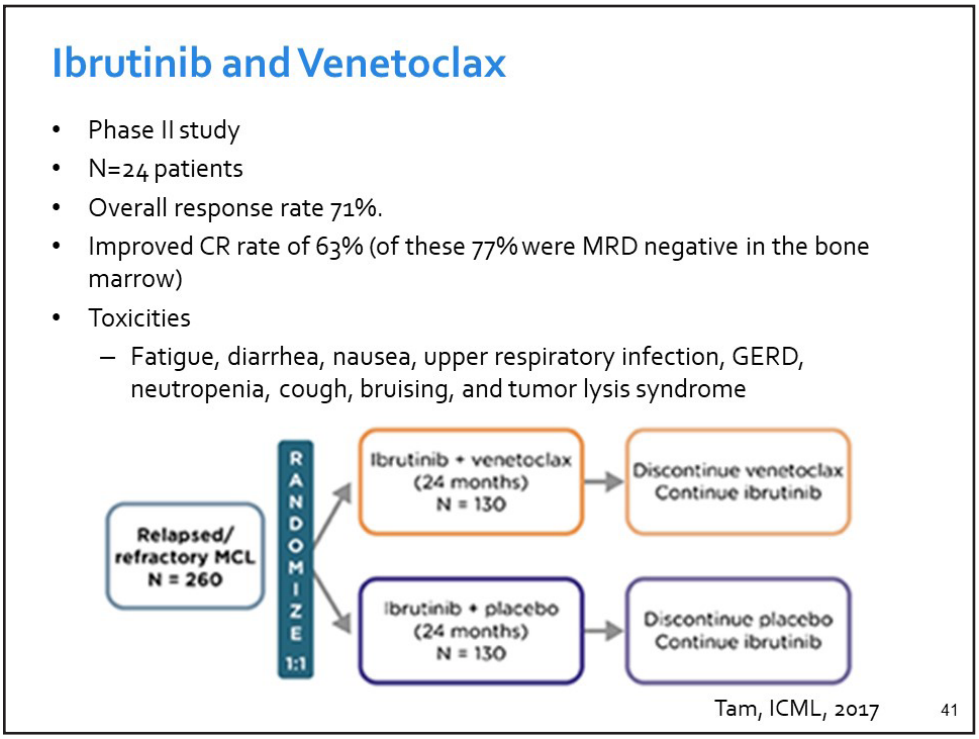
Slide 39. Many new treatment categories for MCL in development…to name a few:

And, so our approach at Memorial Sloan Kettering is to try to think about new combinations that we can use with these new biologically targeted therapies to improve the response rates.



Slide 40. Synergistic combinations of biologically-targeted agents may enhance efficacy in rel/ref MCL

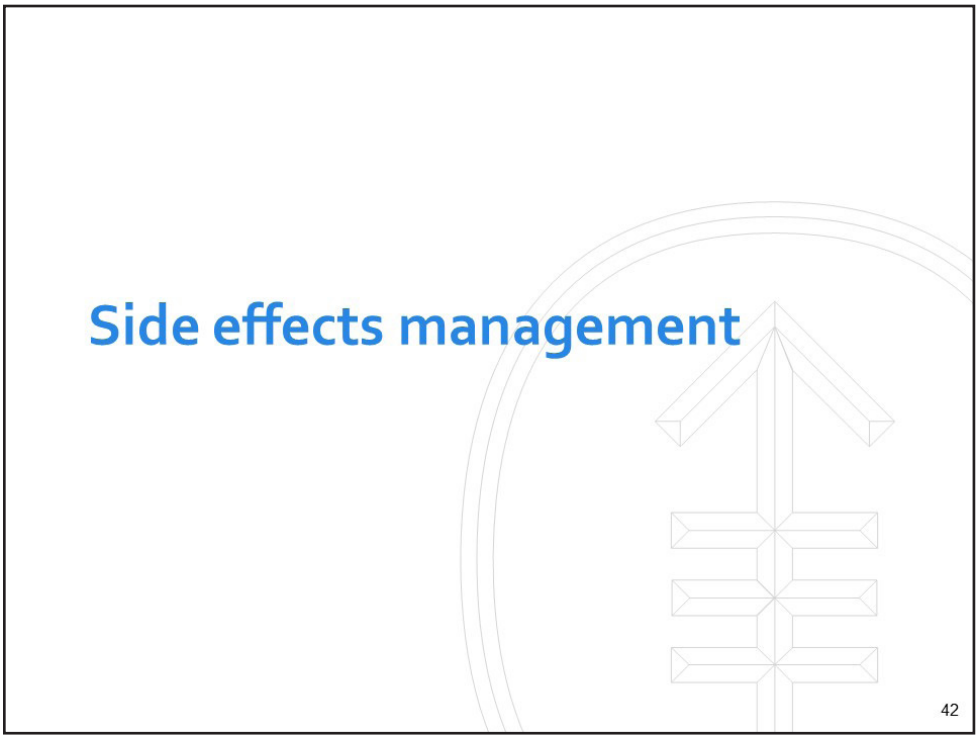
So, one of these exciting combinations is a study that's led by Dr. Batlevi here, which is a Phase I/II study – or Phase IB study – which is combining buparlisib, which is a PI3 kinase inhibitor, and ibrutinib for the treatment of mantle cell lymphoma. And, in this Phase I study, 11 patients with mantle cell lymphoma were treated and the overall response rate was 100%. And, 8 of these 11 patients achieved a complete response so much higher complete response rate and overall response rate than with ibrutinib or a PI3 kinase inhibitor alone. And the reason why we think that's the case is because we believe that dual targeting of synergistic pathways are pathways that both lead to signals to turn on cell growth. If you could potentially block both, you could overcome mechanisms of resistance and improve the depth of response, and that's what we've seen with this exciting study.



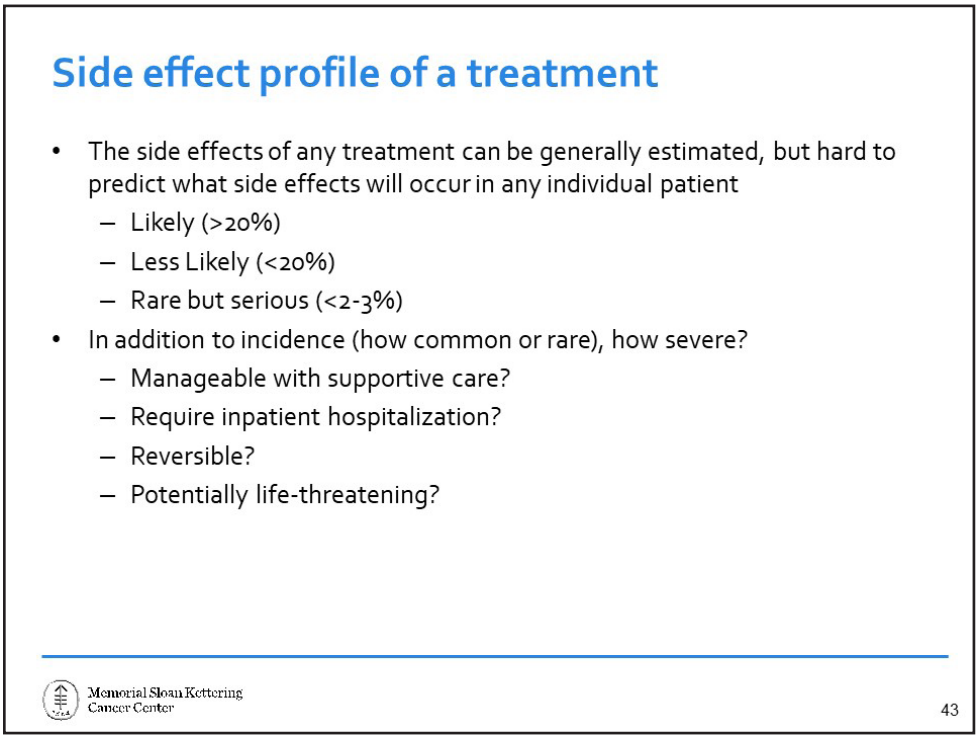
Slide 41. Ibrutinib and Venetoclax

Another combination, which has great potential, is ibrutinib plus venetoclax. The results of this study were presented at the International Congress on lymphoma in Lugano this year in the summer, and 24 patients were treated with ibrutinib and venetoclax. The overall response rate was 70%, but the complete response rate was much higher than with ibrutinib or venetoclax alone. The CR rate was 63%. And, when more sophisticated blood tests and bone marrow tests were done to look to see were there any residual cells left over, this is minimal residual disease testing, they found that many patients were MRD (minimal residual disease) negative with this very exciting combination. So, this suggests that the depth of response and hopefully the duration of response could potentially be much longer with this combination.

Because of these exciting results, there's now a Phase III study that's planned in relapsed/refractory mantle cell lymphoma, that's shown here in the schematic below, which MSKCC is participating in, in which patients will be randomized, relapsed/ refractory mantle cell lymphoma patients will be randomized to receive either ibrutinib and venetoclax, the combination, or ibrutinib alone. And, hopefully what we will see in this randomized study is that the combination wins and is more effective than ibrutinib alone, and this could potentially lead to the FDA approval of this combination.



Slide 42. Side effects management
I'll mention just a few words about side effects.

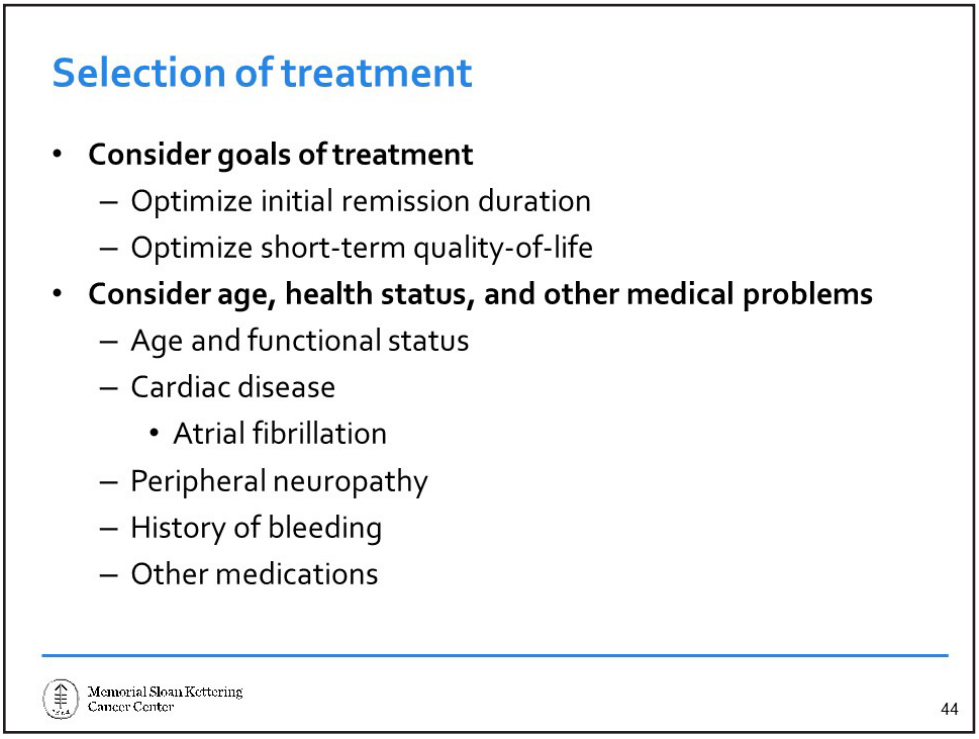


Slide 43. Side effect profile of a treatment

All of these different treatments that I've mentioned have different side effects. But I think as a patient, it's important to think about what side effects are common versus those that are uncommon. And, when you read a consent form you'll see that there're different categories of side effects, those that are likely, these happen in greater than 20% of patients, less likely, less than 20% of patients, and then those that are rare, but serious.

I would encourage you to talk to your medical oncologist about what they have experienced in terms of the tolerability of any given drug or new drugs in a patient. And, how they can try to think about those side effects, particularly in you or in a mantle cell lymphoma patient specifically, because oftentimes, the presence or absence of other medical issues can really influence how somebody tolerates a given drug.

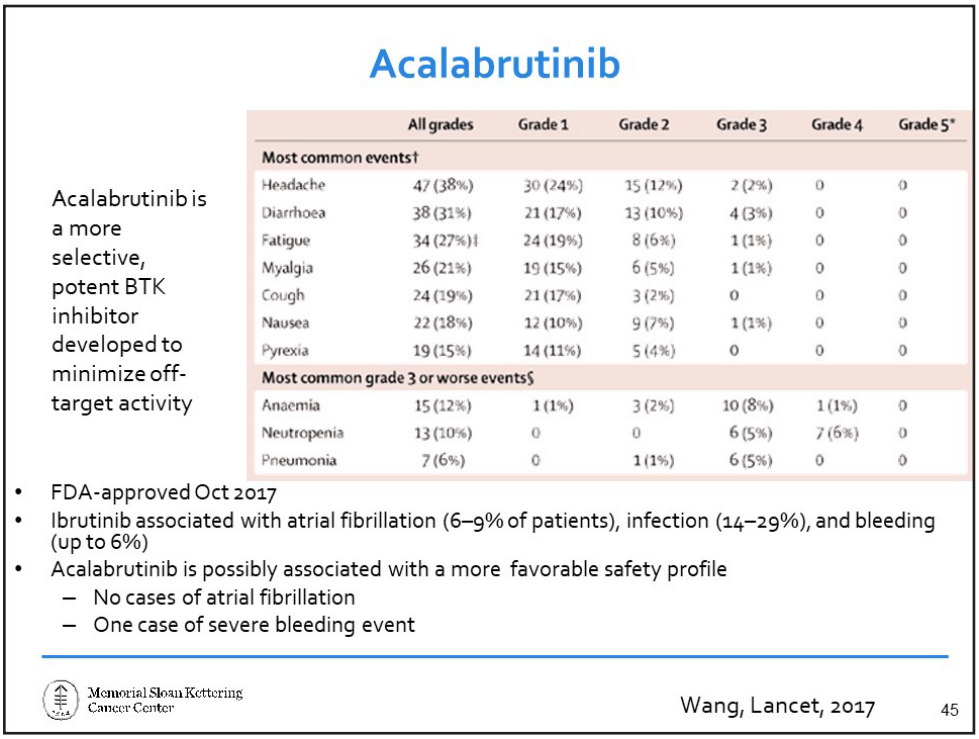
The other things that are important is not only just the incidence, like the percentage of patients who experience the side effect, but also how severe is that side effect. Is, for example, the diarrhea mild and it can be well managed with Imodium, or is it more severe, do patients have to be admitted to the hospital to manage some of the side effects from a treatment, and, are these side effects reversible, are they potentially life-threatening? These are all questions to ask when considering the side effect profile of any given drug.



Side 44. Selection of treatment

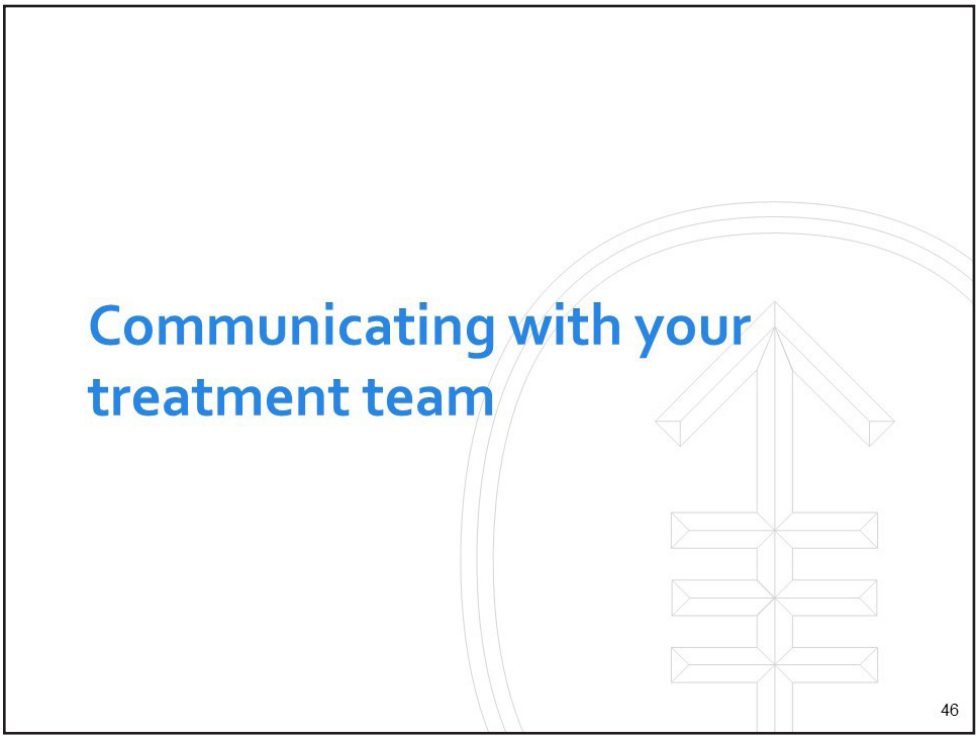
In addition, there are certain things that are important in terms of selecting one treatment over another. One is to think about what your goal with the treatment is. Is it to optimize your initial remission duration or is it to optimize your short-term quality of life? And, that may go into the decision. For example, an initial transplant approach with very intensive induction chemotherapy, that may be associated with the longest initial remission duration, but it's going to require, you know, 9, 10 months commitment to go through intensive chemo and an inpatient hospitalization and the follow-up after an autologous stem cell transplant. So, those things need to be weighed.

And, then also, we always consider age and health status and other medical problems. For example, atrial fibrillation is an important consideration with ibrutinib therapy because ibrutinib can cause the development of atrial fibrillation and also can cause increased heart rates or poor control of atrial fibrillation in some cases. Certain treatments are associated with peripheral neuropathy, such as Velcade® or bortezomib, and that's something to consider. And also, whether or not you're on a blood thinner or have a history of bleeding, those are things to consider with ibrutinib, which puts you at increased risk for bleeding.



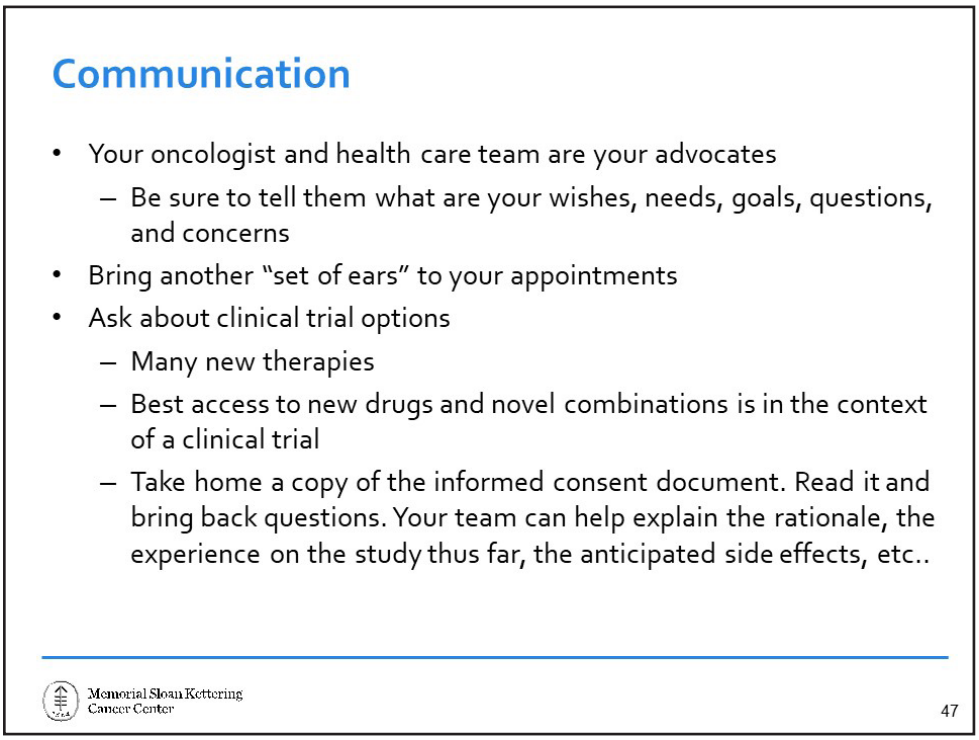
Slide 45. Acalabrutinib

One of the exciting new developments in the treatment of relapsed/refractory mantle cell lymphoma was the recent FDA approval of acalabrutinib. This is another BTK inhibitor. It's a sister drug to ibrutinib. And, it has the same target. But, it's more selective and it has less off-target effects. And, so therefore, it may have fewer side effects compared to standard ibrutinib. And so, what was seen, this was just presented at ASH and recently published in the *Lancet*, is that there seemed to be no cases of atrial fibrillation with acalabrutinib, whereas we see about 6 to 9% of patients develop AFib with ibrutinib. And, there was only 1 case of significant bleeding. So, acalabrutinib may be a very effective BTK inhibitor that limits some of the toxicities that we see with standard ibrutinib.



Slide 46. Communicating with your treatment team

The last few thoughts I would share with the group today is about communication with your treatment team.



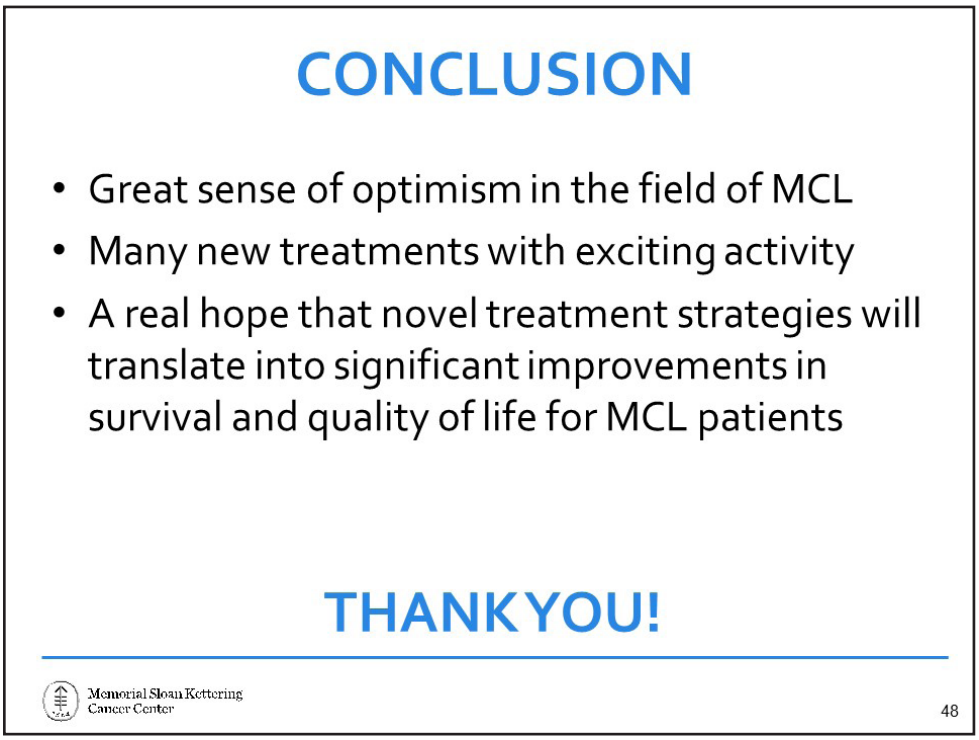
Slide 47. Communication

So, one of the things that I really encourage my patients to share with your oncologist is to tell them what your goals are with treatment because I think this is very important to understand a patient, their context, what their wishes are, and what their concerns are with treatment, in order to really define a personalized treatment approach that is best for that individual patient. Especially with mantle cell lymphoma, where there's not one standard of care, you really want your medical oncologist to understand you and your goals in order to come up with a treatment plan that is best for you.

The other thing I always encourage my patients to do is to bring another set of ears, which just means family or a friend, who can listen to the discussion along with you, potentially take some notes, so that you can discuss the important points after the visit. Because sometimes the visit goes very quickly, and you have a lot of questions or concerns and sometimes it could be useful to review that with somebody who's on your care team.

And, then the other thing is that we really encourage patients to ask about clinical trial options. As you can see, there's a number of new treatments that are in development for mantle cell lymphoma and we are really optimistic about the outcomes improving for mantle cell lymphoma patients, given all of these new treatments. And, so enrollment in a clinical trial is oftentimes a very excellent way to get access to some of these new drugs or novel combinations.

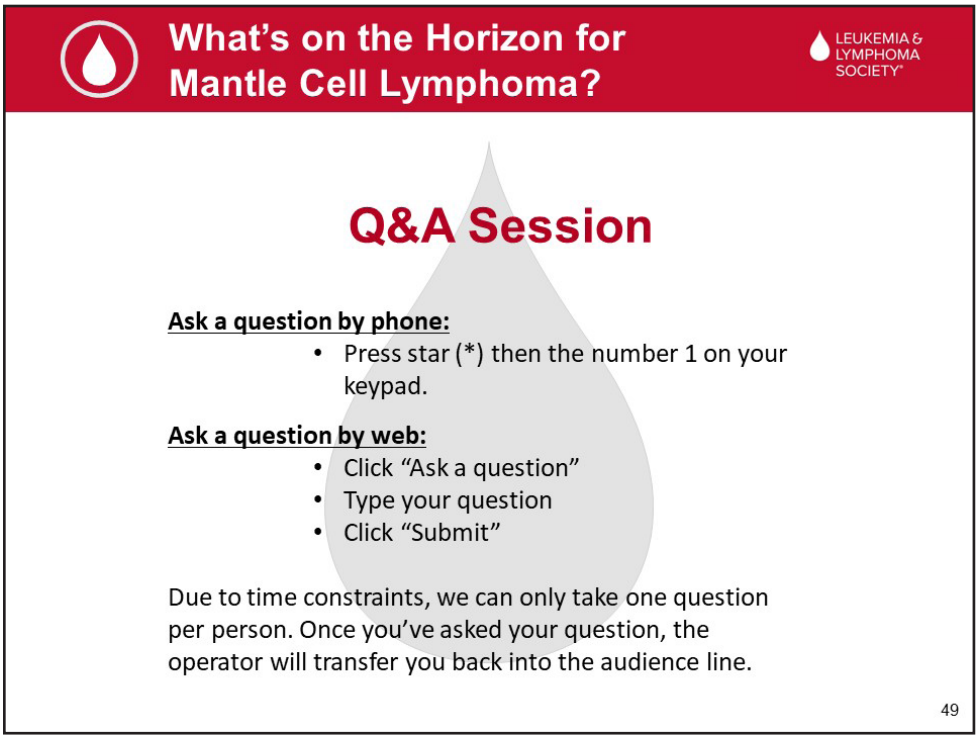
Encourage your medical provider to give you a copy of the informed consent document, take it home, read it, write on it, bring back your questions, and have your team help explain what's the rationale for the study, what's the experience so far on the study, how have patients done, what are the side effects, etcetera. And, that's really the responsibility of your care team to help you to best understand what your treatment options are.



Slide 48. CONCLUSION

So, with that, I will say thank you again and again emphasize that we really have a great sense of optimism in mantle cell lymphoma, there are many new exciting highly active treatments, and we think that this is going to lead to an improvement in the survival and quality of life for mantle cell lymphoma patients in the future.

So, thanks again.



Slide 49. Q&A Session

Lizette Figueroa-Rivera:
Thank you so much, Dr. Kumar, for your very informative presentation. It's now time for the question and answer portion of our program.

We'll take our first question from our web audience. Kimberly asks, what is the overall average remission time before reoccurrence usually starts to show and there are symptoms recognizable other than a CT scan?

Dr. Kumar:
That's a great question. The remission duration really depends upon what is the initial treatment approach that's utilized. So, for the more gentle treatments, for example, like bendamustine and rituximab, the initial remission duration may be shorter than for a patient who receives more intensive chemotherapy and an autologous stem cell transplant.

Overall the remission durations are improving significantly with the incorporation of the novel biologically targeted therapies that I discussed, as well as with increased experience, giving different treatment regimens.

We usually quote for the intensive induction chemotherapy followed by transplant approach, the median or average remission duration is around 7 years or so. With the bendamustine and rituximab, the median or average remission duration is probably closer to 3 to 5 years.

Lizette Figueroa-Rivera:
Thank you. And we'll take the next question from our telephone audience, please.

Operator:
Yes, our next question comes from John from North Carolina. Please state your question.

John:
Yes, I had a remission and a second treatment for – a much briefer treatment about 3 years ago. Since that time, since early 2015, I've been taking ibrutinib. Started out with 4 per day, then 2, and now I do 1 per day because of the side effects. Have had no side effects in about 3 years. And, I just wondered if I should continue to take 1 per day or try to go back to 2 per day and see what the side effects might be.

Dr. Kumar:
Thank you, John. I think in general if a treatment is working for you and is helping to control your lymphoma, then I would say to continue with that treatment. And, so we know from the Phase I data where they looked at pharmacokinetic and dynamic information from ibrutinib, or Imbruvica, that even at a 1 pill per day dosing, there is very effective hitting of the target of Bruton's tyrosine kinase. And, so many patients have very good efficacy even at a lower dose.

Lizette Figueroa-Rivera:
Thank you for the question. And, our next question comes from our web audience. Alexander asks about the latest MCL CAR T-cell therapy, applicable developments, and also if MRD testing, which is minimal residual disease testing, can be an alternative to the maintenance traditional tests, such as PET/CT scans or bone marrow biopsies.

Dr. Kumar:
So those are 2 very good questions. So, we are actively studying CAR T-cells for mantle cell lymphoma. As you know, the FDA approved CAR T-cell therapy for another type of B cell non-Hodgkin lymphoma called diffuse large B cell lymphoma. And, there is an ongoing Phase II study called the ZUMA-2 study that's looking specifically at CAR T-cells in the mantle cell lymphoma population. And so, as a mantle cell lymphoma patient, you certainly would be potentially eligible for a number of different clinical trials at specialized cancer centers, to participate in a CAR T-cell trial. And, it may very well be possible that CAR T-cell therapy in the future will be FDA approved for mantle cell lymphoma. However, we don't know – we don't have enough data to know yet whether CAR T-cells are an effective strategy for mantle cell lymphoma. That data has not yet been presented. There's really only a handful of mantle cell lymphoma patients that have been presented or – and so it's an ongoing area of investigation.

With regard to minimal residual disease (MRD) testing, so that's a very exciting and important way to assess whether there's microscopic or circulating tumor DNA in a patient's bloodstream. And, there are many different MRD – or there's many different clinical trials that are incorporating minimal residual disease testing into the clinical trial design. So, for example, there is a cooperative group study in the United States for newly diagnosed mantle cell lymphoma patients, where they will undergo initial induction chemotherapy and if they become MRD negative, then they will not receive a transplant. However, if they're MRD positive, they will receive a stem cell transplant. And so, MRD is potentially a tool that could be utilized to see what is the depth of response to any particular treatment, and to help guide whether patients can – whether patients need to receive further therapy or whether their therapy could be de-escalated or stopped.

Now, whether MRD blood testing will be able to replace PET scans or bone marrow evaluations, that's something that we don't – we don't have the answer to yet. For now, imaging testing and bone marrow evaluations are the best way to assess the status of your disease.

Lizette Figueroa-Rivera:
And we'll take the next question from our web audience. We actually have 2 people asking about allogeneic stem cell transplant and how does allogeneic stem cell transplant, which is a transplant that utilizes cells from a donor, how does that play a role for mantle cell lymphoma?

Dr. Kumar:
Yes, so there is a role for allogeneic stem cell transplant for mantle cell lymphoma and allogeneic stem cell transplant is potentially an approach that could be curative for some mantle cell lymphoma patients. And typically, we utilize allogeneic stem cell transplants in younger or fit patients who have received initial therapy, but then the disease comes back. And, particularly patients for whom they may have certain high-risk features like we discussed, they may be reasonable candidates for allogeneic stem cell transplant.

The decision whether or not to do an allogeneic stem cell transplant is a very individualized decision and requires meeting a transplant team, assessing what the donor options are. You know, whether you have a sibling donor or matched unrelated donor, cord blood, etcetera. Assessing what the status of one's disease is at the time of the transplant, if you've achieved a remission with subsequent therapy. And also, the health status of the patient in terms of what their age is and what their other medical issues are.

I would just mention that although allogeneic stem cell transplant has been shown in a proportion of patients to be associated with long-term remission durations and potentially a cure when effective, allogeneic stem cell transplants do have more toxicities associated with them, like infection or graft-versus-host disease (GVHD), and so it's very important that your medical team carefully balances the risks versus the benefits. But certainly, we all have patients who are very good candidates for allogeneic stem cell transplant.

Lizette Figueroa-Rivera:
Thank you. And our next question comes from the web from Larry. Larry asks, can initial indolent, which is non-aggressive mantle cell, relapse in the form of blastic, which is aggressive? His relapse occurred in the eye orbit 4 years after a stem cell transplant.

Dr. Kumar:
Yes, yes, that can occur. So, mantle cell lymphoma can evolve in terms of the subtype of mantle cell lymphoma, and can acquire new genetic abnormalities. And, these genetic abnormalities can be associated with more aggressive disease. So, we know that blastic mantle cell lymphoma tends to occur in later stages of the disease, although patients can be initially diagnosed with blastic mantle cell as well. And, we also know that, for example, patients can acquire a P53 mutation later on in their disease course. And oftentimes, that P53 mutation is associated with blastic disease. So, it is common or, you know, certainly we see patients who initially have more favorable disease biology, undergo initial treatment, and then relapse in the future with more aggressive disease.

Lizette Figueroa-Rivera:
And our next question comes from Deanna from the web. She asks, since rituximab maintenance seems to be helpful after transplant, why not continue for more than 3 years?

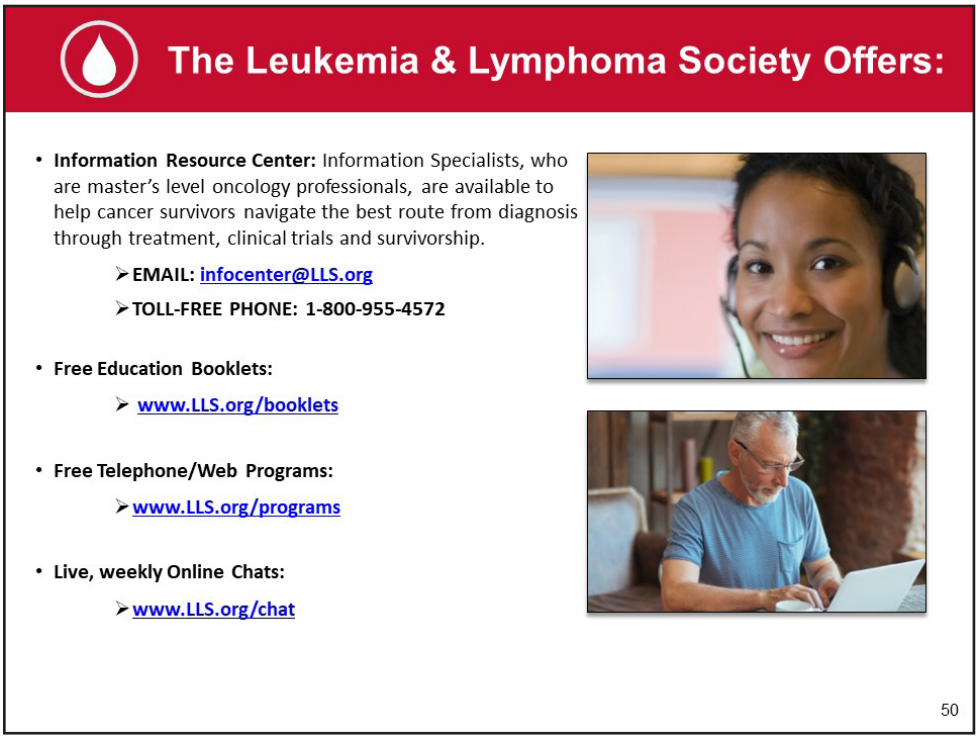
Dr. Kumar:
Well, that's a very good question. We actually don't know what the optimal duration of maintenance is for mantle cell lymphoma. And, we can only use the guide that was published in the study, in the randomized study, and they chose 3 years of maintenance, and so we know what the outcomes are associated with that duration of treatment. We don't know whether the outcomes would be even better if you continued the maintenance, or would potentially be just as good if the maintenance was a shorter duration.

What we do know is that rituximab maintenance over a long period of time can be associated with the development of what's called hypogammaglobulinemia, or low immunoglobulin levels. And, that can sometimes put patients at increased risk for infection, like pneumonia and sinusitis and things like that. So, we always have to balance the interest in optimizing the treatment, but also recognizing that treating people ad infinitum with certain drugs can put them at increased risk for toxicities related to the therapy.

Lizette Figueroa-Rivera:
Thank you. And, our last question today comes from Melissa and she's asking, where do you see the future role of methotrexate in the treatment for mantle cell lymphoma?

Dr. Kumar:
Well, methotrexate is a treatment that's not thought to be one of the standard treatments for mantle cell lymphoma, except for when mantle cell lymphoma involves the central nervous system (CNS). So, it's a small percentage of patients who have mantle cell lymphoma that involves the brain or the spinal cord or the fluid around the brain and the spinal cord, that's called central nervous system involvement. And, if patients do have CNS involvement with mantle cell lymphoma, then intravenous methotrexate can be a very effective therapy for that particular presentation.

Lizette Figueroa-Rivera:
Thank you, Melissa, for your question, which was our final question today. And thank you so much, Dr. Kumar, for your continued dedication to patients.



Slide 50. The Leukemia & Lymphoma Society Offers: Information Resource Center

For those of you who participated in today's program, we hope the information presented today will assist you and your family in your next steps.

If we weren't able to get to your question today or you want more information, you may speak to an Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time, or reach us by email at *infocenter@LLS.org*.

Slide 51. The Leukemia & Lymphoma Society Offers: Support Resources

Information Specialists are available to answer your questions about treatment, including clinical trials, and answer other questions you may have about support, including financial assistance for treatment.

Again, we'd like to thank AstraZeneca Pharmaceuticals, Celgene, and Pharmacyclics, an AbbVie Company, & Janssen Biotech for support for this program.

Dr. Kumar, thank you again for volunteering your time with us today. And, on behalf of The Leukemia & Lymphoma Society, thank you all for joining us. Goodbye and we wish you well.

END