How Is Mantle Cell Lymphoma Treated?

Operator
Greetings, and welcome to "How is Mantle Cell Lymphoma Treated, a live telephone and web education program. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you. You may begin.

Ms. Lizette Figueroa-Rivera
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Special thanks to Dr. Bijal Shah for sharing his time and expertise with us today.

Before we begin, our President and CEO, Dr. Louis DeGennaro, will make some remarks.

Louis DeGennaro, MD
I'm Dr. Louis DeGennaro, President and CEO of The Leukemia & Lymphoma Society. I'd like to welcome all of the patients, caregivers, and health care professionals attending the program today. At The Leukemia & Lymphoma Society, our vision is a world without blood cancers. Since we started in 1949, LLS has invested more than $1.2 billion in breakthrough research to advance lifesaving treatments and cures.

We've played a pioneering role in funding many of today's most promising advances, including targeted therapies and immunotherapies that have led to increased survival rates and improved the quality of life for many blood cancer patients.

Though LLS is known for funding groundbreaking research, we do so much more. As this program demonstrates, we are the leading source of free blood cancer information, education, and support for patients, survivors, caregivers, families, and health care professionals. We also support blood cancer patients in their local communities through our chapters across the country, and we advocate at the state and federal level for policies to ensure that patients have access to quality, affordable, and coordinated care.

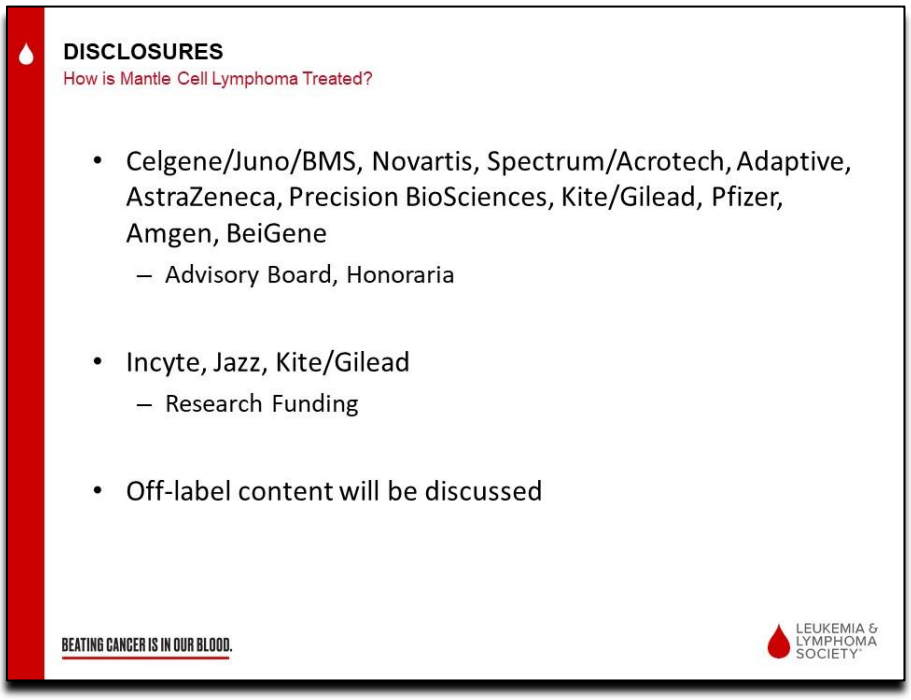
We're committed to working tirelessly toward our mission every single day. Today, you'll have the opportunity to learn from esteemed, key opinion leaders. They each have volunteered their time, and

we appreciate their dedication to supporting our mission—their commitment to caring for patients living with blood cancers. Thank you for joining us.

Ms. Lizette Figueroa-Rivera
I want to take this time to thank everyone for participating in today's program during these uncertain times. All of our COVID-19 support services, including COVID-19-specific webcasts, podcasts, online chats, as well as our new COVID-19 patient financial aid program and information regarding COVID-19 are on our website at lls.org/coronavirus. If you want to speak to us directly, please call us at 1-800-955-4572. Let us be here for you.

Support for this program is provided by Kite Pharma, Inc.; Pharmacyclics, an AbbVie Company; & Janssen Biotech.

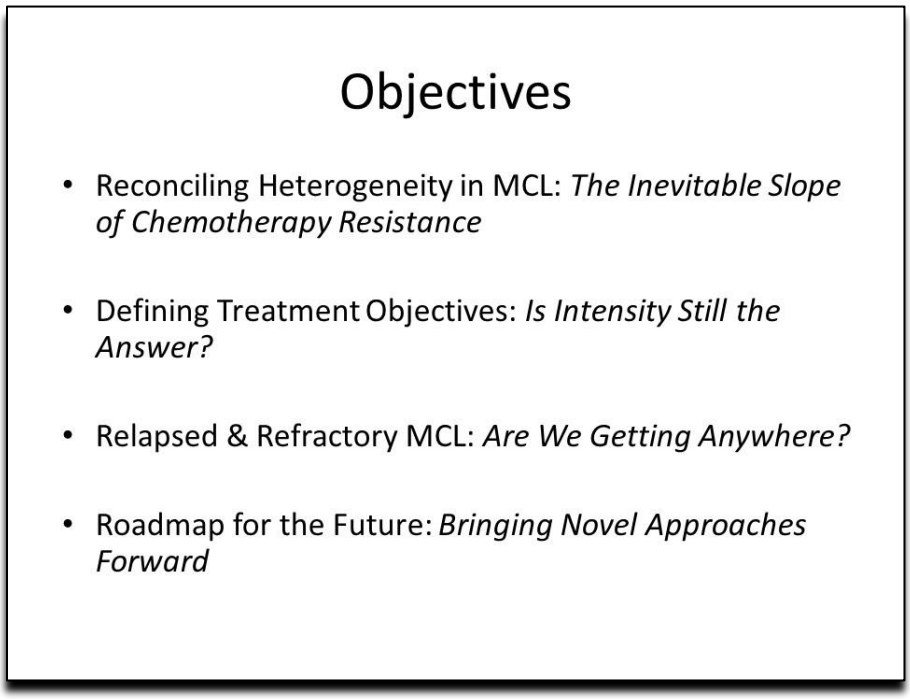
I am now pleased to introduce Dr. Bijal Shah, Associate Member, Department of Malignant Hematology at Moffitt Cancer Center in Tampa, Florida. On behalf of The Leukemia & Lymphoma Society, thank you so much for volunteering your time and expertise with us. Dr. Shah, I'm now privileged to turn the program over to you.



Disclosures

How Is Mantle Cell Lymphoma Treated?

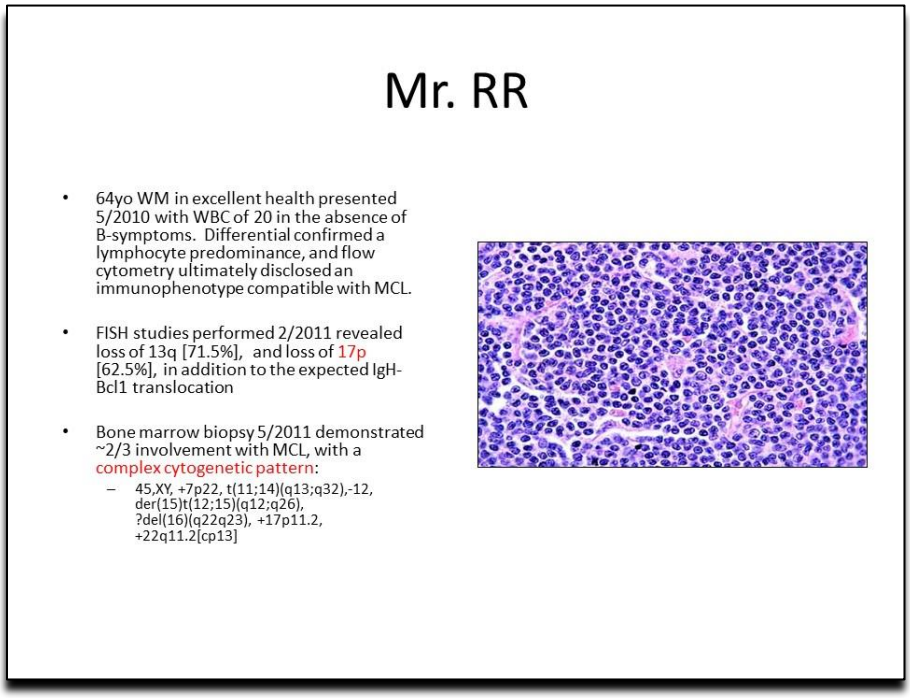
Bijal Shah, MD
Hi. Thank you for having me, and thanks for all the folks who have decided to spend their Wednesday afternoon hearing me talk a little bit about mantle cell lymphoma. I'm going to focus a little bit on treatment, but I don't think we can really discuss treatment without talking a little bit about the biology of mantle cell. What makes it what it is? And how then do we use that insight to guide the therapies that we give?



Objectives

With that, the objectives that I like to review in this talk—and I've shared this talk with others in the past before with a few updates, of course—but trying to talk a little bit about how wildly heterogeneous mantle cell is.

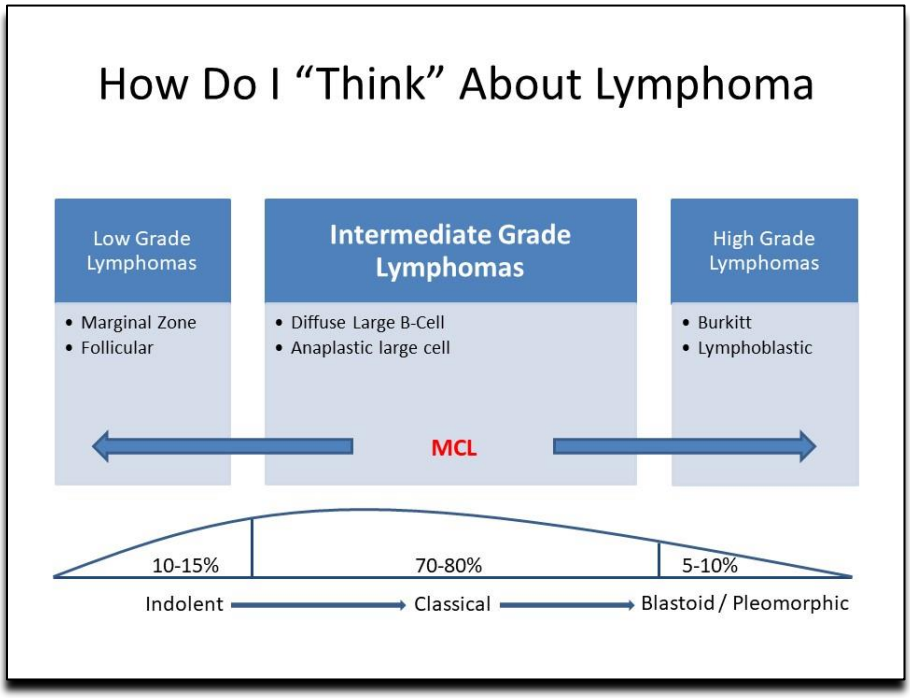
It's amazing that for a disease that I thought would be simple, how very different people can present and how very different their course of disease can be over time. Trying to understand how aggressively we need to treat in this day and age, as we've now developed very new and very exciting therapies, trying to understand how best to manage relapsed and resistant mantle cell lymphoma. And hopefully tease you guys with some very exciting, novel developments that I think are going to make the treatment of mantle cell even more encouraging, even more hopeful, even more exciting.



Mr. RR

I always like to start with a case. And this is an amalgam of a few cases that I took care of. But Mr. RR, he presented to me in his mid-60s and he had an elevated white cell count. He did not have any other symptoms did not have any enlarged lymph nodes, had mild enlargement of the spleen. But when we really look to understand what is again the biology of his mantle cell, we saw that he had a lot of genetic changes that made us nervous.

And I've highlighted some of them here and I'll talk about them more in the presentation. But the question then being, "What do we do now?" Seeing that here's a person coming to us who otherwise feels good but with high white blood cell counts and a pattern of genetic changes that are worrisome? So, I think the first thing that I should probably talk about is how I think about lymphoma more broadly.



How Do I "Think" About Lymphoma

When I started training with Eduardo Sotomayor, who is now the Cancer Center Director at George Washington University. This is the instruction I received from him. We broke down our lymphomas into three broad groups: low-grade lymphomas, which are slow growing and incurable. But more often people will experience inconvenient relapses but not ones that are life-threatening. And so we would often tell people, "You'll die with the lymphoma rather than as a result of the lymphoma."

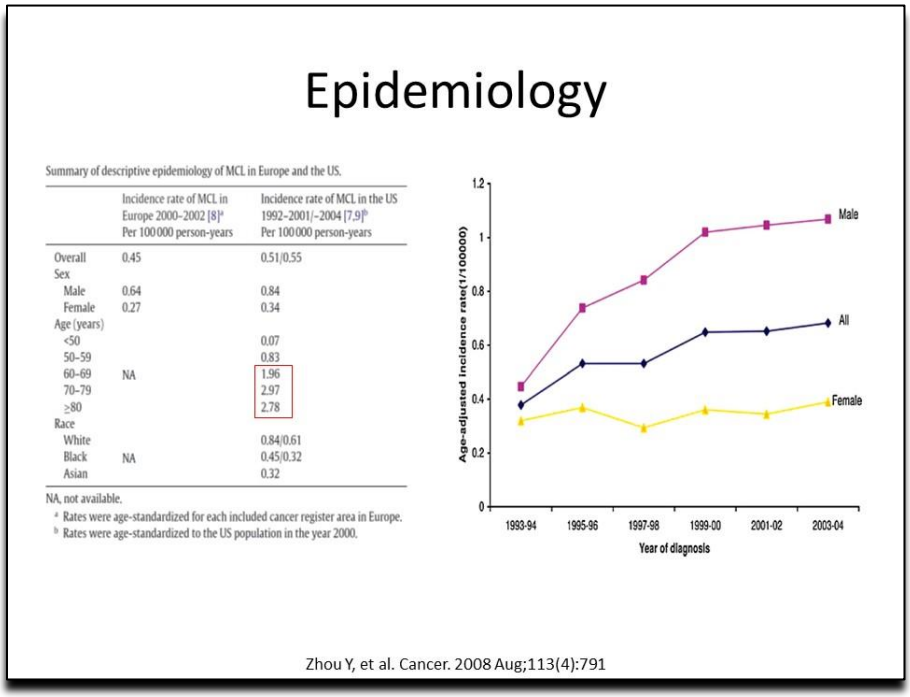
As we move into more rapidly growing lymphomas, we talk about our intermediate-grade lymphomas, and these are ones that we can cure. And because we can cure them, we tend to push a little bit harder. As we go into our high-grade lymphomas, we talk now about Burkitt lymphoma, acute lymphoblastic leukemia, or acute lymphoblastic lymphomas. And these are a tougher breed to treat, but we are making strides. With that said, we still treat with curative intent. But we often have to push more aggressively with our chemotherapy to achieve that objective.

So then, where does mantle cell fall in all this? And this is the hard part. It falls all throughout the spectrum. We can see indolent or slow-growing cases that behave a lot like a marginal zone or a follicular lymphoma. We can see aggressive cases that grow more quickly. And then we can see very highly aggressive cases that we refer to as blastoid or pleomorphic mantle cell lymphoma that will behave almost like an acute lymphoblastic leukemia in terms of its aggressiveness and its rapid rate of growth.

Unfortunately, regardless of which category the mantle cell falls into, what we find is that it remains incurable. Now, I say this with a little bit of a grain of salt, recognizing that there are rare cases that I have seen that are in ongoing remission after their first line of therapy, now 10 or even 15 years out. But I want to make it clear that I think that's the exception rather than the rule. More often, the mantle cell will come back.

And as the arrows at the bottom of the screen demonstrate, we tend to progress from a more indolent or slow-growing mantle cell to one that's a little bit more aggressive to one that can be highly aggressive over time. Now, whether that's really truly a reflection of the mantle cell lymphoma changing per se or whether it's just a reflection of the mantle cell becoming resistant to therapy, much the same way that bacteria can become resistant to different antibiotics, I think is a harder question to

answer. But it is this trend over time towards more resistant disease that can make the treatment of mantle cell more difficult.

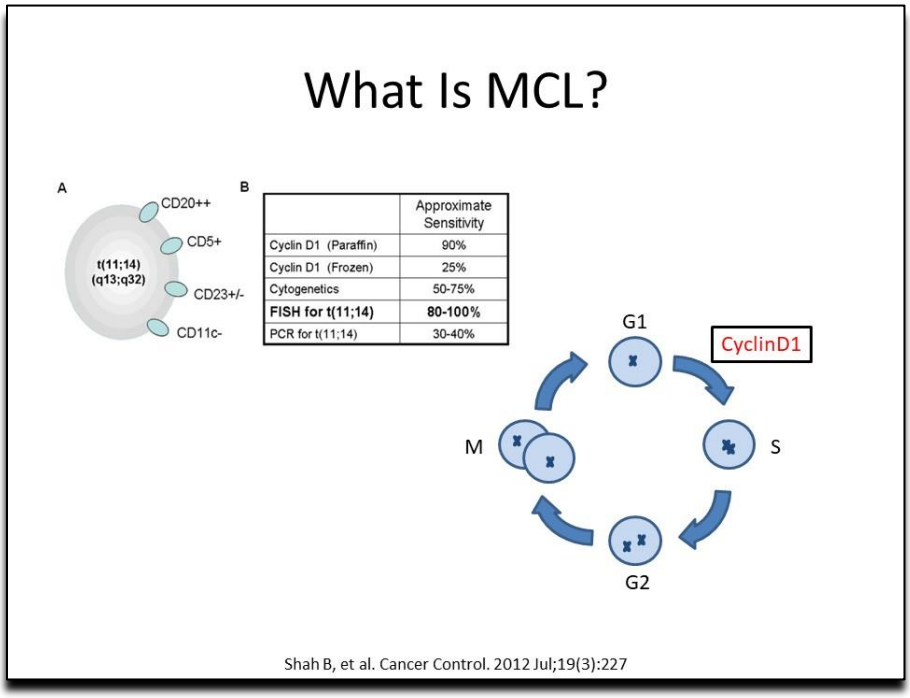


Epidemiology

I do like to talk a little bit about the epidemiology of mantle cell lymphoma. And this is a study from 2008 that just nicely highlighted—one—that mantle cell does appear to be increasing in its incidence. And I don't think it's because there's some terrible exposure out there that's driving the rate of mantle cell up. I think it's because we've gotten much, much better at diagnosing it.

There were some lookalikes. There's a condition called chronic lymphocytic leukemia, which is one in particular. We've gotten much better at distinguishing who has mantle cell from who has these other conditions, and I think that's why we're seeing this increase in the rate of mantle cell lymphoma.

The other thing that I highlighted with the box in red is mantle cell lymphoma is by and large a lymphoma that occurs in our mid- to late-60s. The median or the middle-point mark for mantle cell lymphoma is about 68 years of age. And you can see that it does tend to increase in frequency as people get older.



What Is MCL

So then, what is mantle cell? We can start by talking about some of the markers that we use. And we use these that are called CD markers or clusters of differentiation. And these are just different proteins that are present on the surface of the mantle cell lymphoma to help us decide, "Is this likely to be mantle cell or not?" CD5, in particular, is one we see very commonly. CD20 tends to be overexpressed in mantle cell lymphoma.

But where we really get to the heart of picking up on those cases of mantle cell lymphoma is digging a little deeper, digging into the genetics. And there is a change that is going to occur in well over 98% of all mantle cell lymphoma patients. And this is a change involving two important genes. And again, genes are in our DNA and what direct the cells to make different proteins.

But what we see here is the gene for the immunoglobulin receptor. This is part of how a B cell—which normally produces antibodies—part of how a B cell recognizes bacteria or anything else that it should be fighting. We see that immunoglobulin rearranged with a protein called cyclin D1. Now, what is the rearrangement? Literally, what we're seeing is the cyclin D1—and I'm going to talk a little bit about what that is in a minute—gets accidentally moved from where it should be to a different part of the DNA.

Now, it's juxtaposed or really put under the control of this immunoglobulin receptor. And if you think about it from that standpoint, the whole B cell's job is—right?—to see bacteria, to see viruses, to see whatever is foreign and see it through that immunoglobulin receptor and produce antibodies to help protect us from that threat. Well now, cyclin D1 falls under the same control. And what is the consequence? Now, we get a marked increase in cyclin D1 protein.

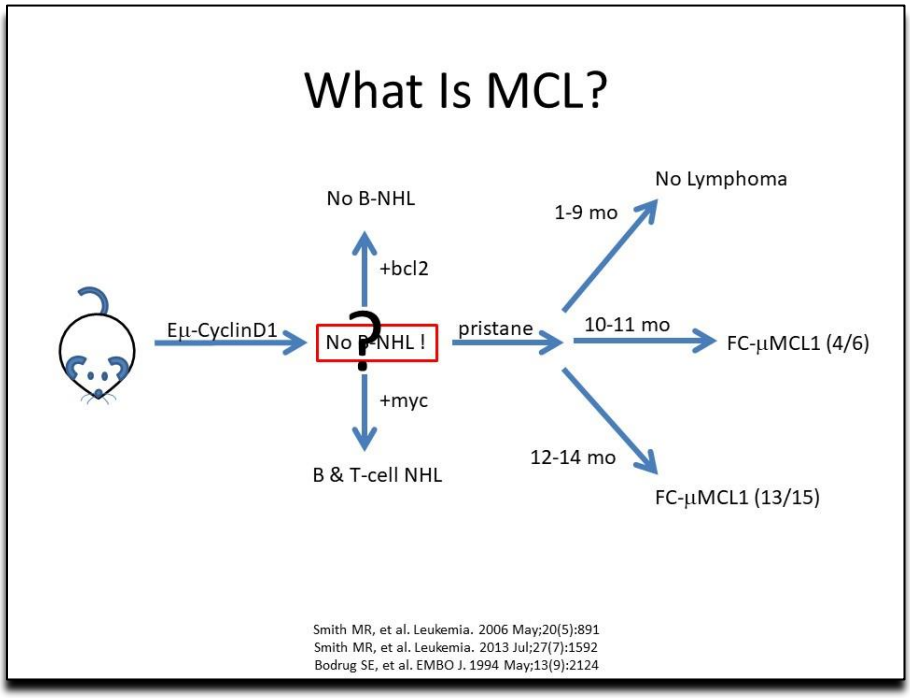
Well, one thing we can take advantage of—because of that rearrangement—we now have tools, one in particular called FISH, which can selectively identify that juxtaposition, that genetic change, to help us say, "Yes, you have mantle cell." So, we're not just now restricted to proteins on the surface of the cell. We can look a little deeper to the inside of a cell.

So, what is cyclin D1? Why is it so important? When we think about the normal life cycle of a cell, it's going to be sitting there resting, not doing much. But at some point, it's going to make the decision, "I

need to grow and make a copy of myself. I need to go from one cell to two cells." As it embarks on that process, this cyclin D1 protein forms what's called a checkpoint. If it's not there, the cell cannot embark on that process.

So, the cyclin D1 essentially is a critical checkbox for the cell to say, "I will not begin the process of cell division, of making a copy of myself, unless there's enough of this present." Now, as it turns out, cyclin D1 is way more complicated than that. It has other things that it does. It participates in DNA repair, it also can protect the cell from undergoing a type of cell death called apoptosis.

So, there are other things that cyclin D1 does as well. I won't go into that as much. I want to give you first this general flavor because I think where it really gets interesting, knowing now that this is present—that this is probably the initial change in folks with mantle cell lymphoma. I want to talk about what we learn next.



What Is MCL?

Well, what do we do? We tried to put cyclin D1 into mice. We put it in all of the mouse's B cells. So now, just like in mantle cell—you know what? The cyclin D1 will only be expressed in those B cells. And what we should see in mantle cell lymphoma—correct? Except we didn't see any of lymphomas. We saw nothing. So, we said, "Well, you know what? It's probably that we need more than just cyclin D1. There are other genetic changes we see in lymphoma. Let's put those in and see if we can get some mantle cell lymphoma."

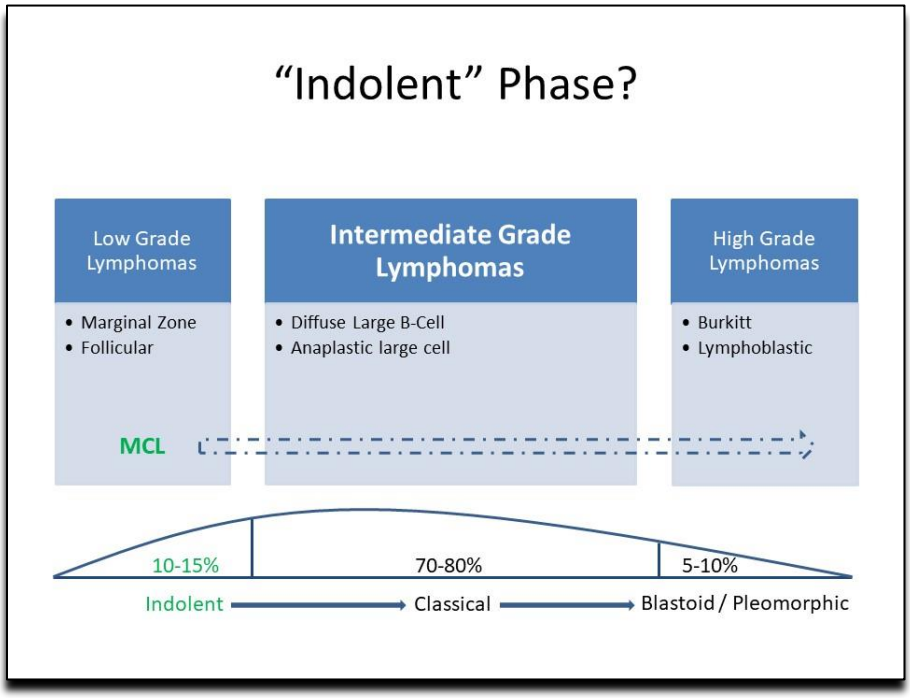
And so, I talked to you about apoptosis a minute ago. BCL2 was a protein very important in that process, and we didn't see any B-cell lymphomas when we added that. We added another one called MYC, and we saw a whole host of both B and a different type of non-Hodgkin's lymphoma called T-cell lymphomas. But we didn't see anything that clearly resembled mantle cell.

So, a really bright guy—he was at the Cleveland Clinic, now at George Washington University—Mitch Smith--said, "Well, maybe we need an inflammatory trigger." Okay, we know that there's this chemical pristane, which can really drive B cells. We didn't see pristane by itself cause a different condition called myeloma, but what if we add this inflammatory drug on this background of mouse B cells that have too much cyclin D1?

And you know what? Nothing happened. But as the arrow indicates, there was something. And this is where I think I'm really impressed. They waited a little while. And they said, "Well, what if we let the mice age, and now we add this inflammatory trigger?" Now, they're seeing some of the mice—about four out of the six—develop something that looks like an aggressive variant of mantle cell lymphoma. Well, what if they get older? Now, we see an even higher percentage.

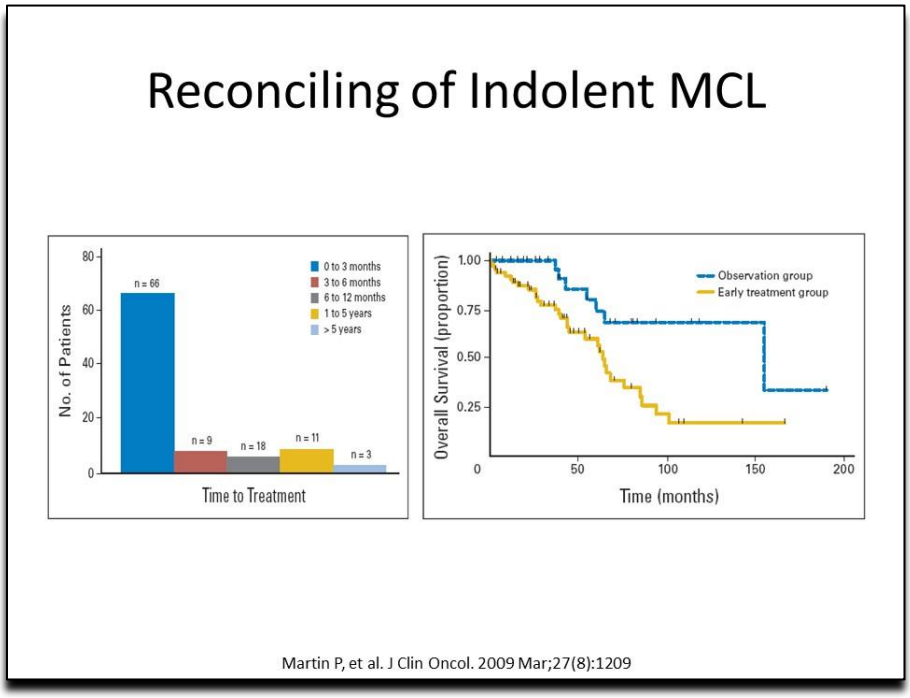
So, what does this story tell us? Yes, the cyclin D1 is really important in the biology of mantle cell lymphoma. But we need at least two other ingredients: one, we need something—some kind of inflammatory trigger or some kind of additional trigger to drive those cells—and two, we need age. And all the changes that occur throughout the mouse—it's not just in the mouse B cells but in their entire immune system. We need a whole variety of other changes to occur to ultimately see this development of mantle cell lymphoma.

So, sometimes people ask, "Is mantle cell inherited?" No, I don't think so. There is some data out of Sweden to say maybe there's an increased tendency for some families to develop mantle cell lymphoma. But what I suspect, more likely, is that there are exposures—think of them in the same kind of category as pristane—that are shared between family members. And that may be what's driving this pattern of seeing lymphomas, particularly mantle cell lymphoma, in a family. And why do I say that? Because I've seen things that I don't understand, like husband and wife—not biologically related—developing mantle cell lymphoma.



"Indolent" Phase?

So, let's talk a little bit about this indolent phase—right? Where the mantle cell lymphoma is behaving more like a follicular or marginal zone lymphoma. Again, this is going to be about 10% to 15% of the patients that I see in my clinic. And the initial hint that we got that there was an indolent variant of mantle cell lymphoma came out of Weill Cornell. And you can see here that most of their patients were treated right at the get-go, within 3 months of being seen.



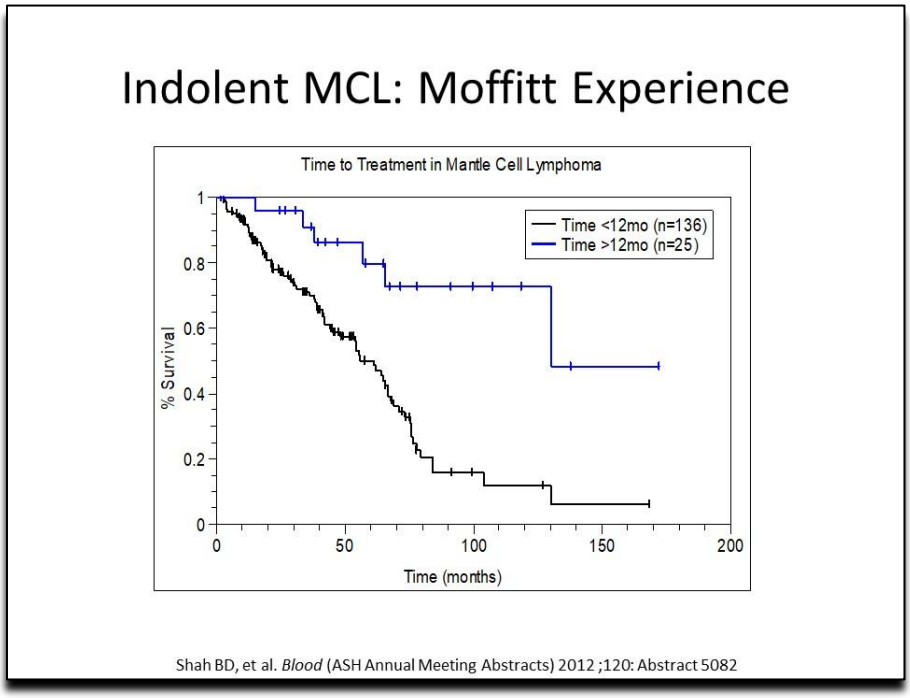
Reconciling of Indolent MCL

But there was this smattering of folks who didn't require treatment right away. In some cases, in this particular study, three patients had gone greater than 5 years without needing any therapy. And so, they simply asked the question, "Is there any harm with this?" And this is the first slide where I'm presenting what's called a survival analysis.

And what these curves essentially reflect is the proportion of people who are alive over time. And so, the percentage of people will drop over time, as you would expect in any group of human beings. We can't live forever. But we paid close attention to that rate at which survival drops.

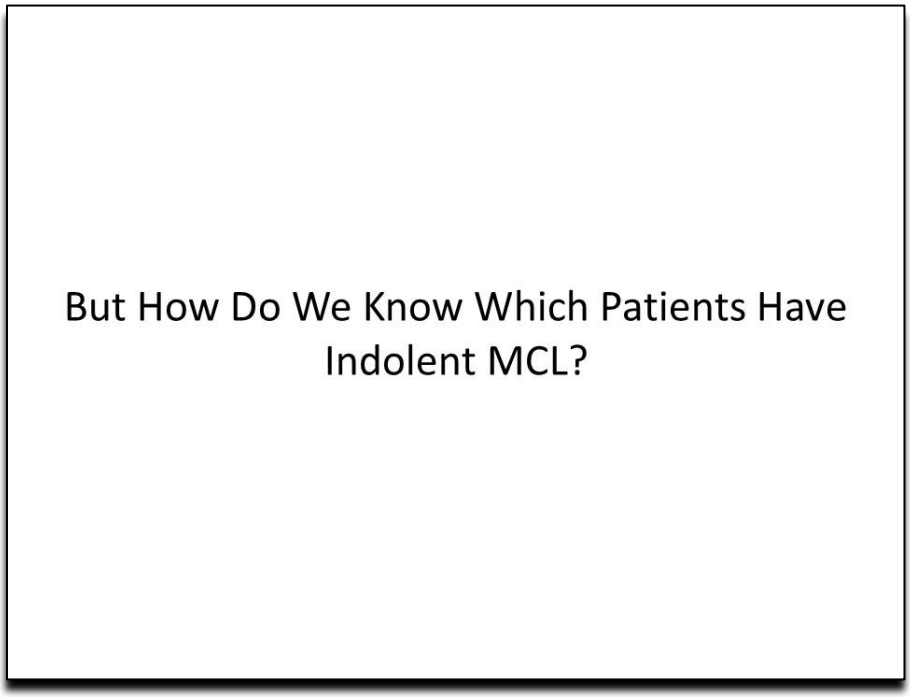
And you can see here, that in this particular series of patients, that the yellow line—people who were treated right away—about half of them were still alive at 5 years. Interestingly, the group that was observed, there was no detriment. There was no decrease in survival. By watching them, we did not do them any harm.

There's another interesting observation, which is when they did need treatment you can get a hint here that their survival looks a lot like those who were treated from the get-go. Does that mean treatment is bad? No, no. These people needed treatment. That's why they got it. What it does mean, though, is that there is this indolent phase where we can watch individuals until their mantle cell progresses to more of a classical variant.



Indolent MCL: Moffitt Experience

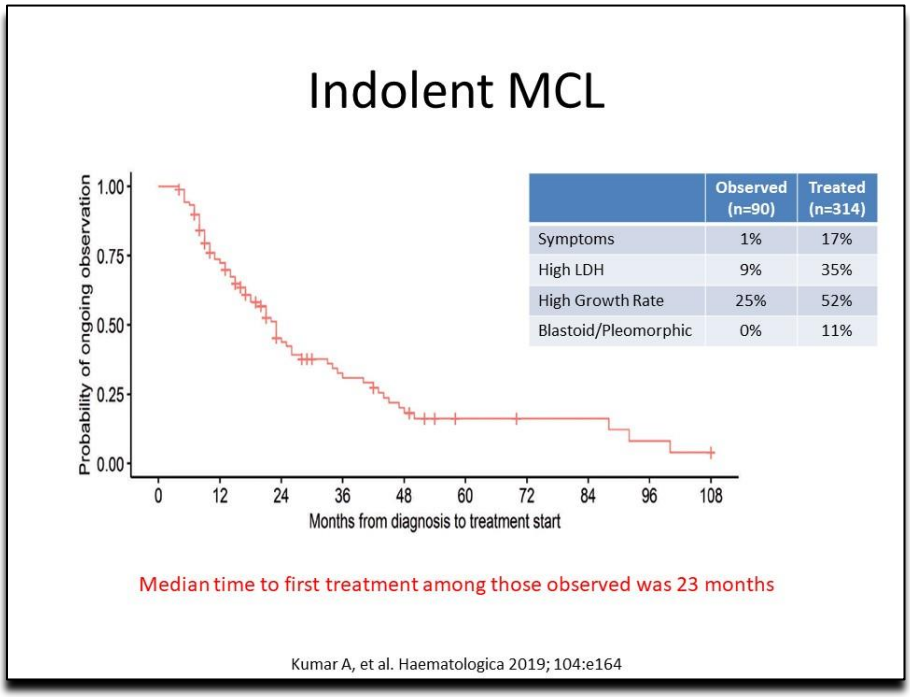
This is just data from Moffitt Cancer Center, showing the same. And for us, that period that seemed to discriminate more indolent from patients who needed treatment right away was about 12 months of watching, suggesting that this group in particular may do substantially better than those who need treatment right at the get-go.



But How Do We Know Which Patients Have Indolent MCL?

But how do we know which patients have Indolent MCL? And they simply said, “What were the characteristics of those who were observed versus those who need to be treated right away?” And what you see here is those who

were observed tended to have no symptoms. And symptoms can be things like fevers, night sweats. It can be a big spleen because mantle cell likes to grow there. It can be low blood counts.



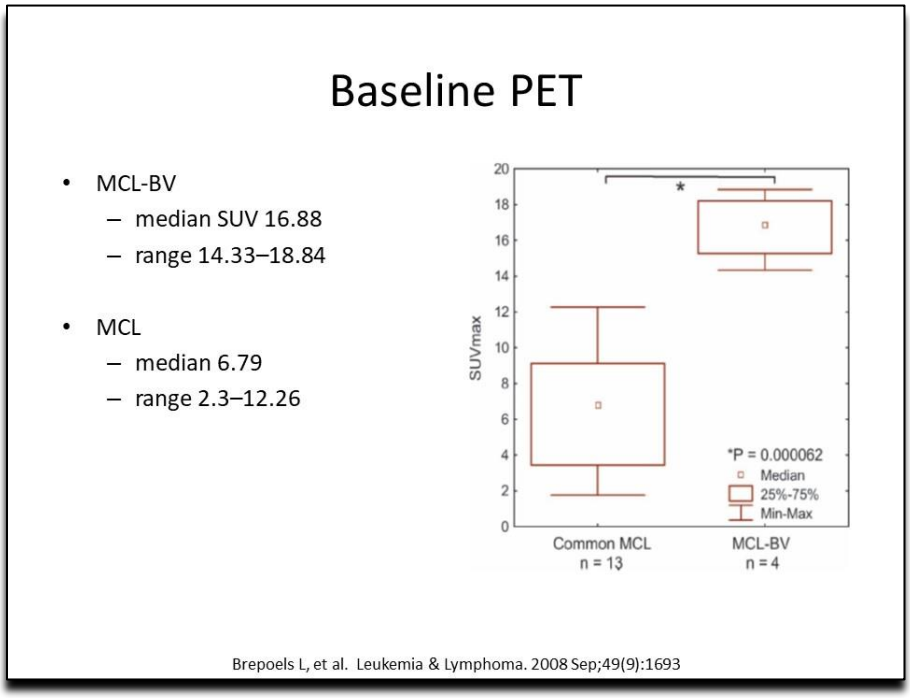
Indolent MCL

But essentially they were asking, "Hey, are you having symptoms?" And if the answer was "yes," well, of course, our goal is to help people not only live longer but feel better. And so, those patients would be treated. They wouldn't be watched. A high LDH is not cholesterol. It stands for lactate dehydrogenase. What we think—and this is not a fact—but what we think is that when mantle cell is growing more quickly, it's having to do so with less oxygen than it would like. Think of it as the growth rate exceeding the supply that it needs to support its growth.

With that, we usually see a production of lactate, an acid. But lactate is not very forgiving to cells. And so, we think that one of the ways the cells compensate is by producing lactate dehydrogenase to turn that lactate into another benign substance—or more benign substance, I should say.

And so, high LDH tends to come with a higher growth rate, and a higher growth rate is also more commonly seen in those with very aggressive mantle cell, which we refer to as blastoid or pleomorphic mantle cell. And so, what you see here across this table is folks who don't present with a high growth rate—and I'll talk a little about what that means a few slides later—without changes under the microscope that we call blastoid or pleomorphic, which indicate more aggressive mantle cell, without high LDH. Those individuals could be observed.

And when they were observed, we could observe them for almost 2 years. Half of them almost made it to the 2-year mark before needing any therapy. And so again, this is that same kind of a survival curve, looking over time to say, "What is the proportion, in this case, of folks who are still being observed? Are there other clues that we can get?"



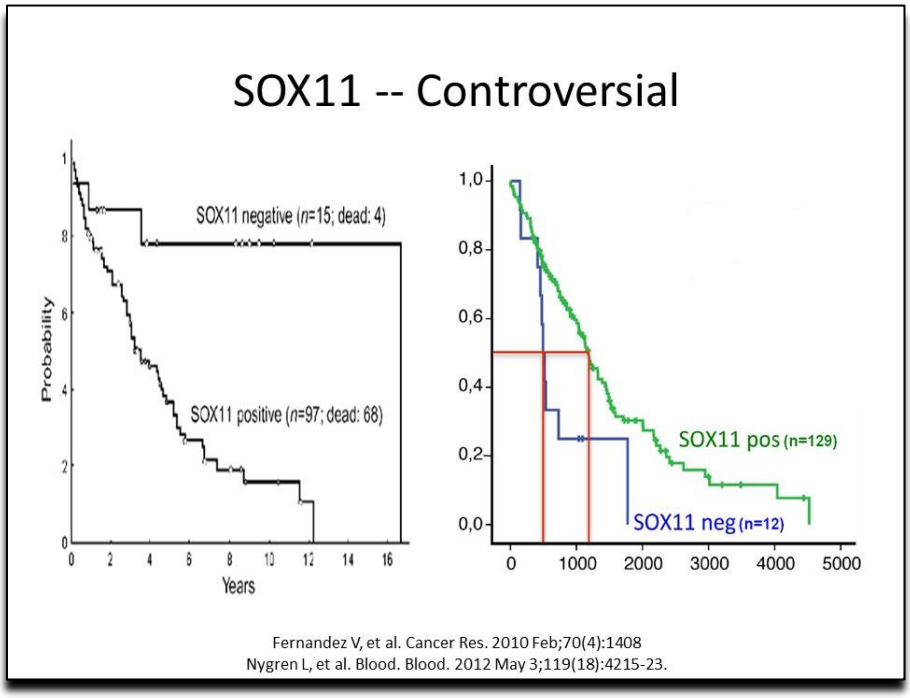
Baseline PET

We tried using PET scans. And PET scans can help discriminate those who have a much, much more aggressive blastoid-type presentation, but it's less helpful in trying to decide who has indolent mantle cell. So, do I use PET scans? Yes, I do. But here I'm now more using it to say, "Where do I put my needle for my biopsy," or, "Where do I tell my surgeon to go and biopsy to get that lymph node," to try and get the best flavor for the most aggressive site of my patient's disease.

Gene Expression Profiling

We have tried to look at something called gene expression profiling. Simply put, I told you that genes, their job is to turn into proteins. And so, we're looking at that intermediate step to say, "Okay,

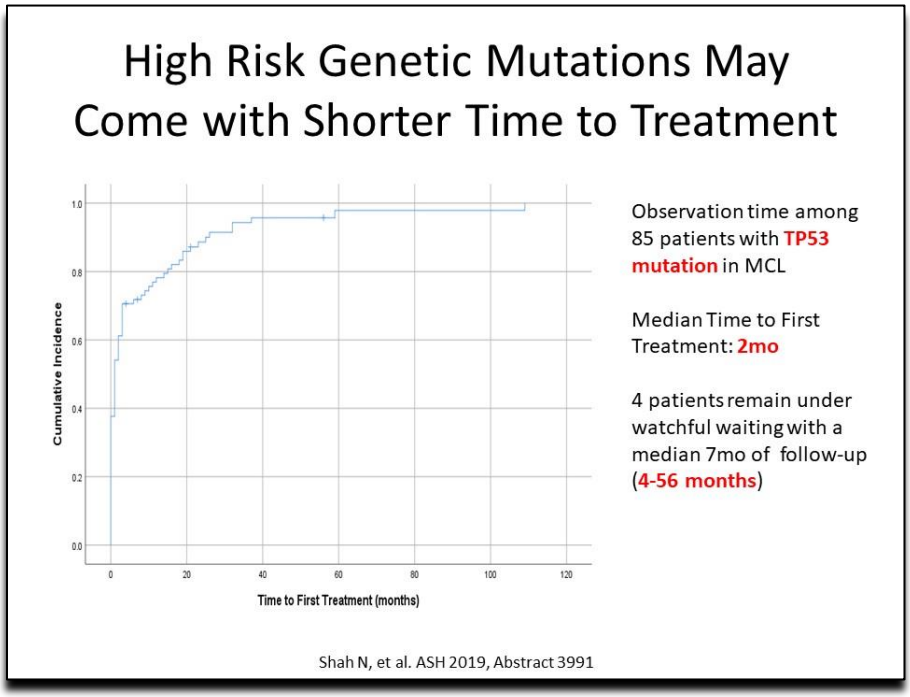
well, if the genes are trying to make proteins, what comes up as a consequence?" And this particular study by one of our larger Spanish groups tried to say, "Hey, we know these patients have more indolent or less aggressive mantle cell lymphoma because we've been watching them for years. Can we find any differences in those genes that are being turned into proteins, between those individuals and those who need treatment right away?"



SOX11 -- Controversial

And there was one really interesting protein that came out called SOX11, which we normally don't see in B cells. And so, they decided to focus on that as saying, "Hey, if we see low SOX11, could that be indicative of someone who has more indolent mantle cell?" And on the left, you see that's what they saw. But, I want to be clear: It's more complicated than that.

And so, different groups have shown different things in terms of what SOX11 means in terms of the biology of mantle cell lymphoma. But I wanted to include it in here because it is often part of the diagnosis of mantle cell. We often include it as one of those proteins that we're looking for to help us understand whether this is mantle cell.

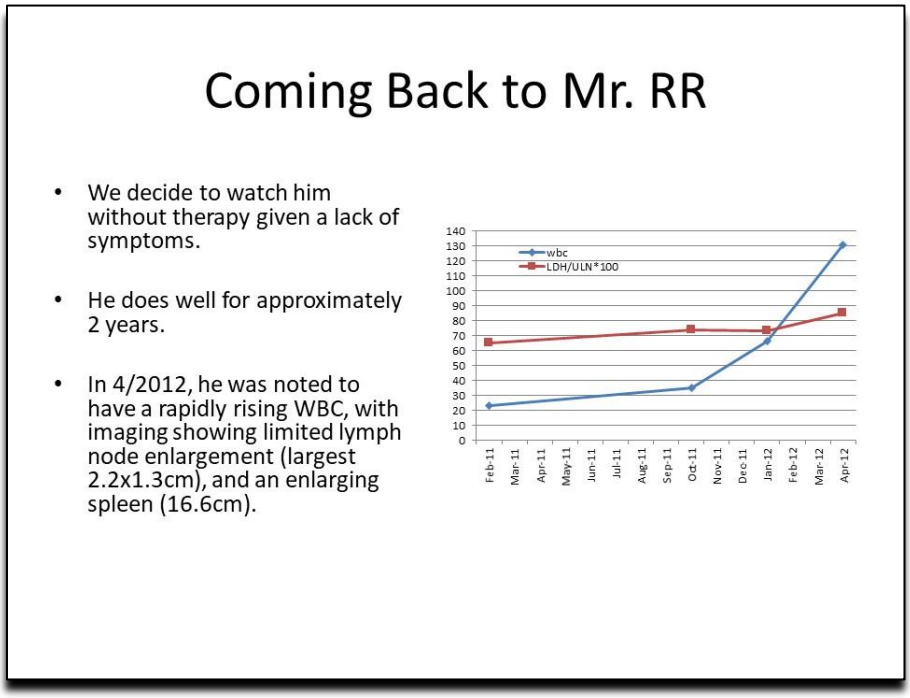


High Risk Genetic Mutations May Come with Shorter Time to Treatment

What about genetic changes? And you're going to hear me talk about TP53 as we go forward. But TP53 is a very important protein in allowing a cell to sense that there is too much genetic damage. And if it does, the cell commits suicide. And the problem being that because our chemotherapy works mainly by trying to induce genetic damage mainly by trying to push them—what we call—over the edge, so that this TP53 goes up. And the cell is now forced to essentially commit suicide. What does it mean if there is no TP53? What does it mean if it's mutated and it doesn't function?

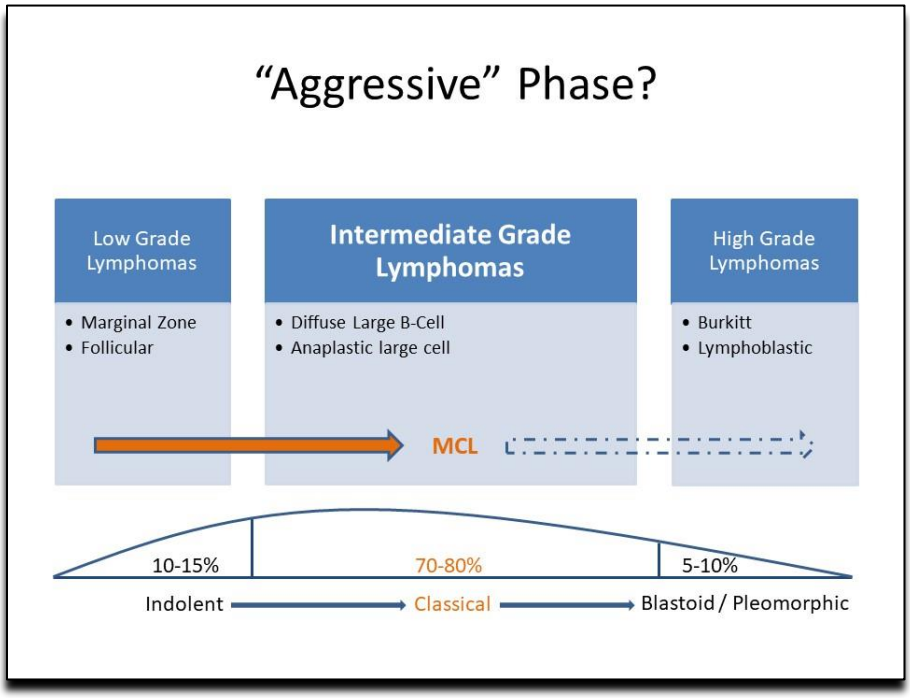
Well, now we know they will be less chemotherapy sensitive because that's in part how chemo works. But does that mean that those individuals will also show just spontaneously higher rates of progression to more advanced disease? And the answer is, it's less clear. We did see that folks who had TP53 mutations this is around 85 patients or so—were more likely to be treated close to presentation, so within about 2 months.

But we also saw several patients—four in this particular series—who have gone on almost as long as 5 years without needing therapy. So, it's probably not just as simple as saying, "Hey, you have a TP53 mutation, so we must treat you." We've seen similar data in CLL as well.



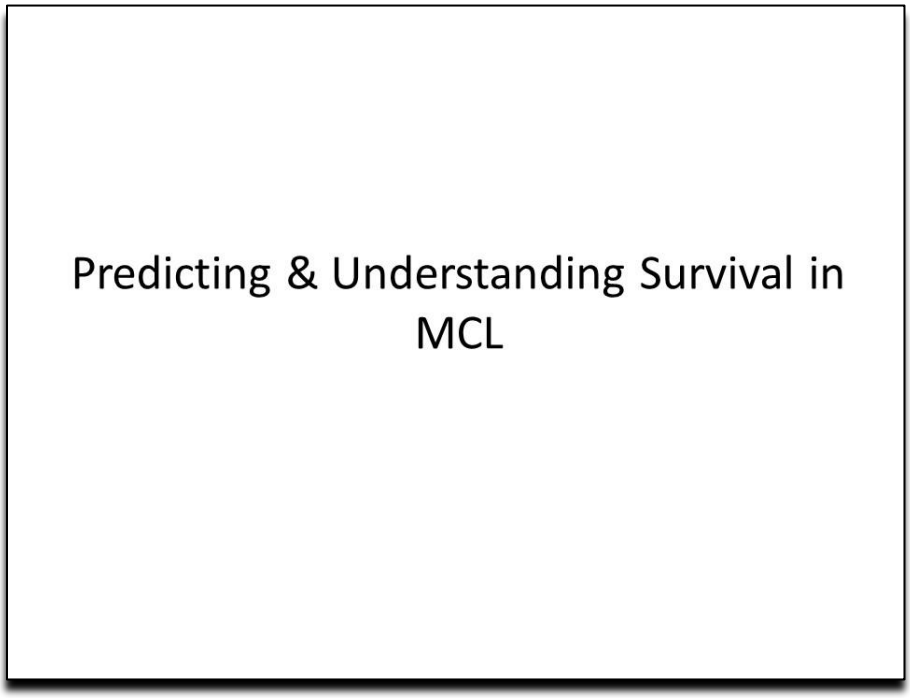
Coming Back to Mr. RR

So, coming back to Mr. RR, we did watch him. And do you know what? He did well for 2 years without needing any therapy. And his blood counts were entirely stable, and he didn't have a symptom in the world. But he did ultimately progress. He was found to have a rapidly rising white cell count—which I've tried to show here—his LDH was rising. He was now developing large lymph nodes, and his spleen was getting even bigger.



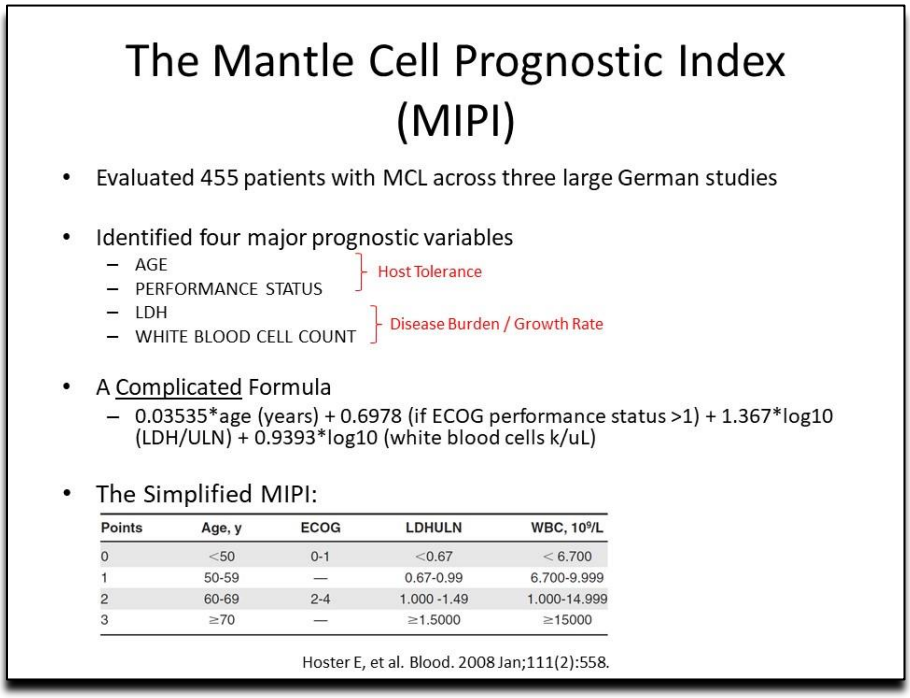
"Aggressive" Phase?

So, now what do we do, right? Now we're here. We're no longer in the indolent phase, we're in the aggressive phase. And so, we know we're going to need therapy at this point.



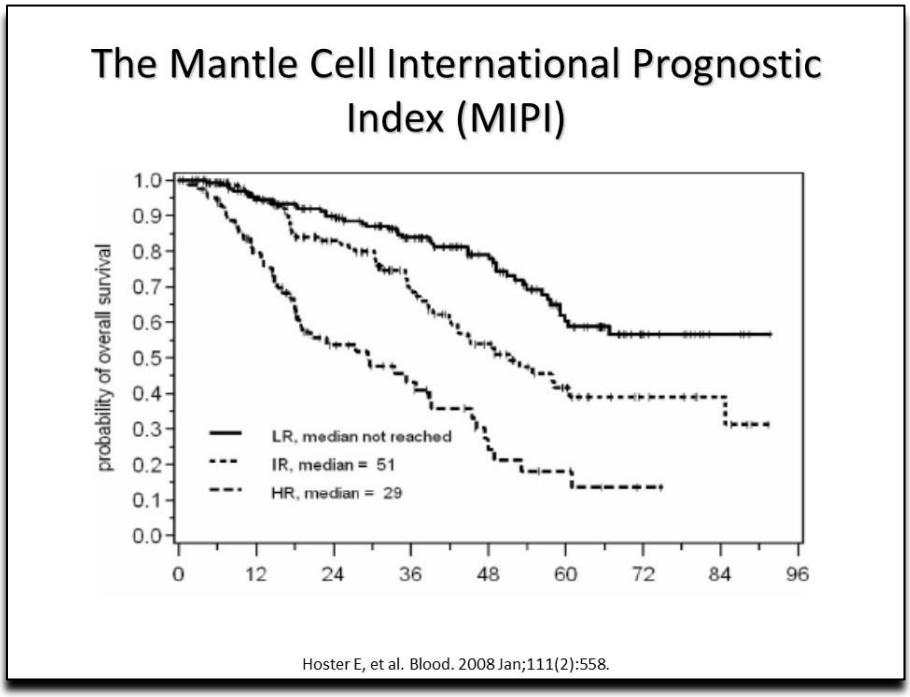
Predicting & Understanding Survival in MCL

So, one big question is, "How do we figure out treatment? How do we figure out—importantly before we even begin—treatment expectations?"



The Mantle Cell Prognostic Index (MIPI)

Our first hint came from the Germans. So, the Germans put together several of their trials to try and ask, "What are those risk factors that are associated with overall survival?" And they came up with four broad categories: age; performance status, which means how active is somebody through the day; LDH, that same marker I told you about; and their white blood cell count. It's a complicated formula.

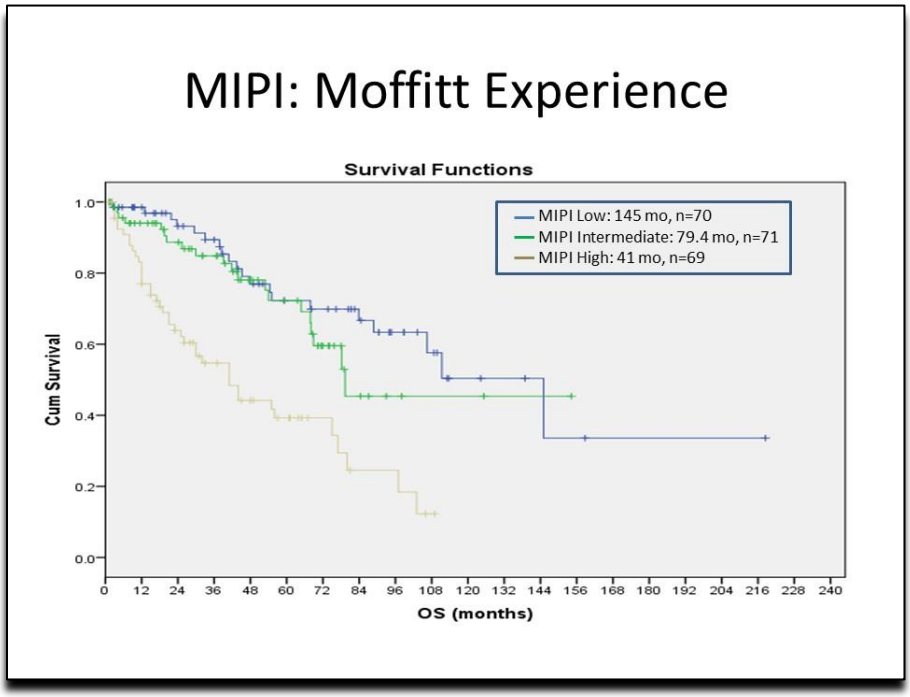


The Mantle Cell International Prognostic Index (MIPI)

But really what are we talking about measuring? Two things. How well can people tolerate particularly intensive therapies, and how much disease do they have? How much mantle cell is in their body, and

what is the growth rate that we think is associated with that? And so, with these two factors, in this is called the Mantle Cell International Prognostic Index.

And I don't want you to pay attention to the actual probability of being alive at 5 years or anything like that because this has already improved dramatically with time. But I do just want to show you that we were able to carve out three broad groups: a low-risk, an intermediate-risk, and a high-risk group. But there are some peculiarities about this curve. And one of those is just how closely that low- and intermediate-risk group sort of ride together before they kind of separated at about 2 years.

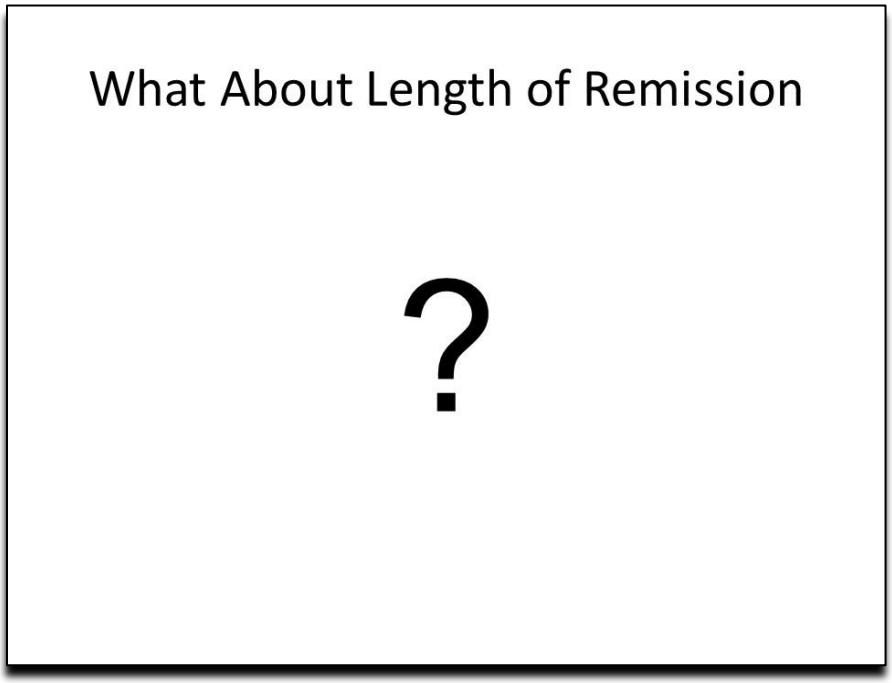


MIPI: Moffitt Experience

And so, one question is, "Are we really where we need to be with this?" We saw very similar things. When we tried to discriminate amongst our patients—how does this Mantle Cell International Prognostic Index perform? We really had a lot of difficulty saying who is low risk and who is intermediate risk. And in fact, in most of my studies, I just lumped the two of them together.

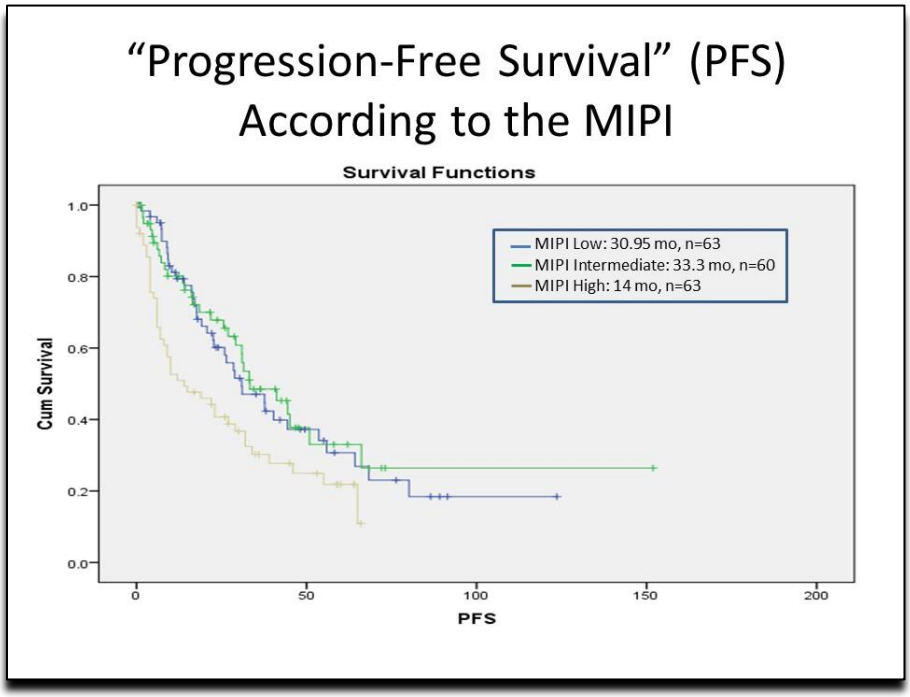
The high risk are definitely high risk. And remember, you would expect older individuals to pass away sooner. You would also expect those who are older and more frail who have multiple other medical problems or who just have just extraordinarily aggressive disease to pass away sooner from their disease relative to those who don't have those characteristics.

One really cool thing, though, that I like to point out with this curve is this median survival—this concept of what is our 50% mark? And what we could see in our low- and-intermediate risk patients if we merged them together is we're talking about a median survival now. So, half of the patients are living about 10 years or longer. And that is something that's very important to stress in mantle cell lymphoma because there's a lot of information on the Internet to suggest that everyone with mantle cell is performing like this very high-risk group. And that's simply not the case.



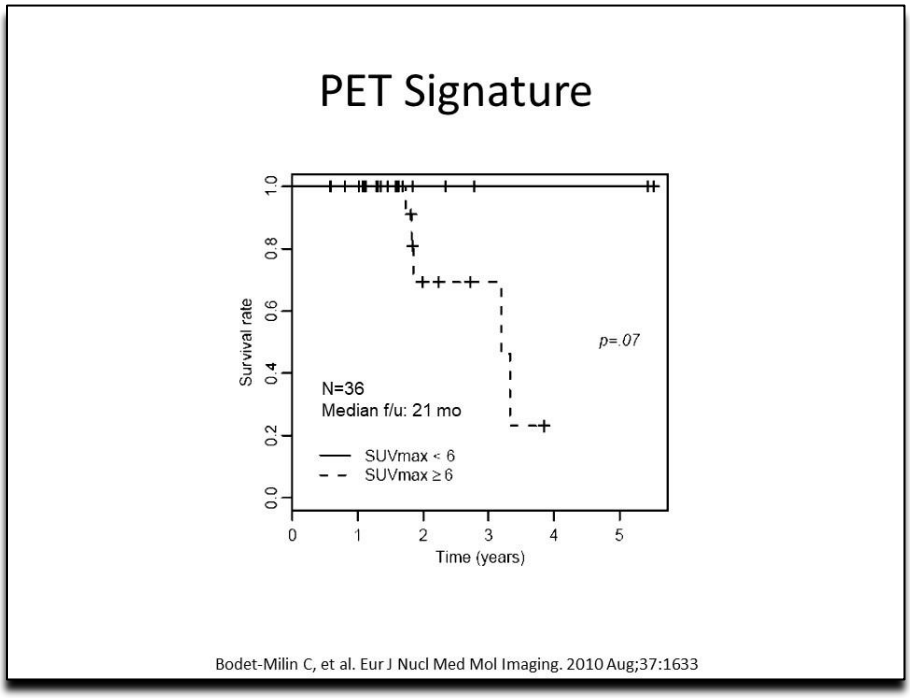
What About Length of Remission

So, what about the length of remission? We don't know. That's a much, much harder thing to predict.



"Progression-Free Survival" (PFS) According to the MIPI

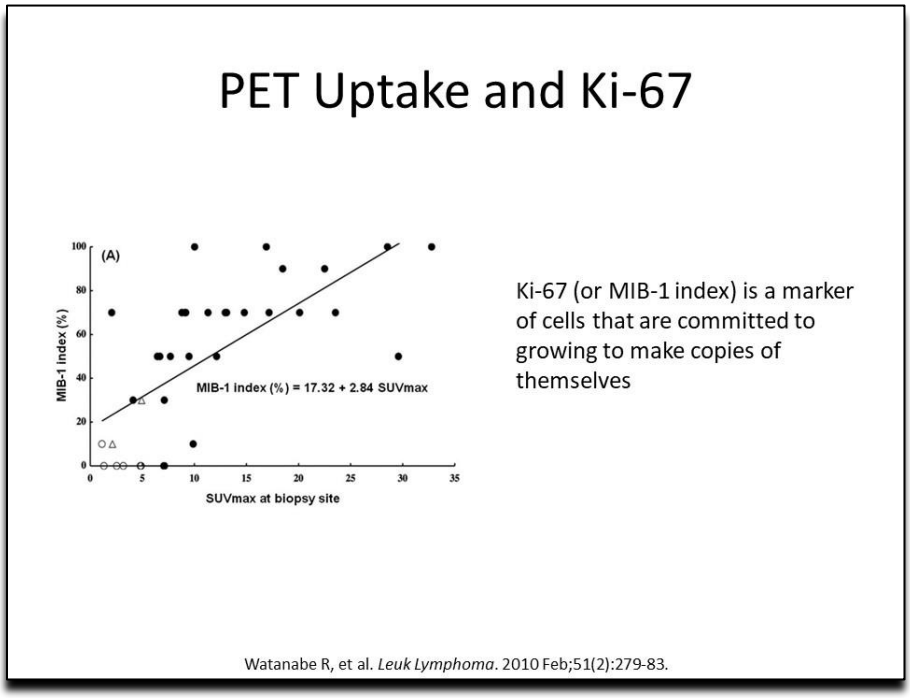
We did try looking at length of remission according to the Mantle Cell International Prognostic Index. And you can see that the higher-risk individuals maybe didn't do as well. But it really wasn't clear that the length of remission was up to that very first line of therapy was as clearly associated with how long people would live.



PET Signature

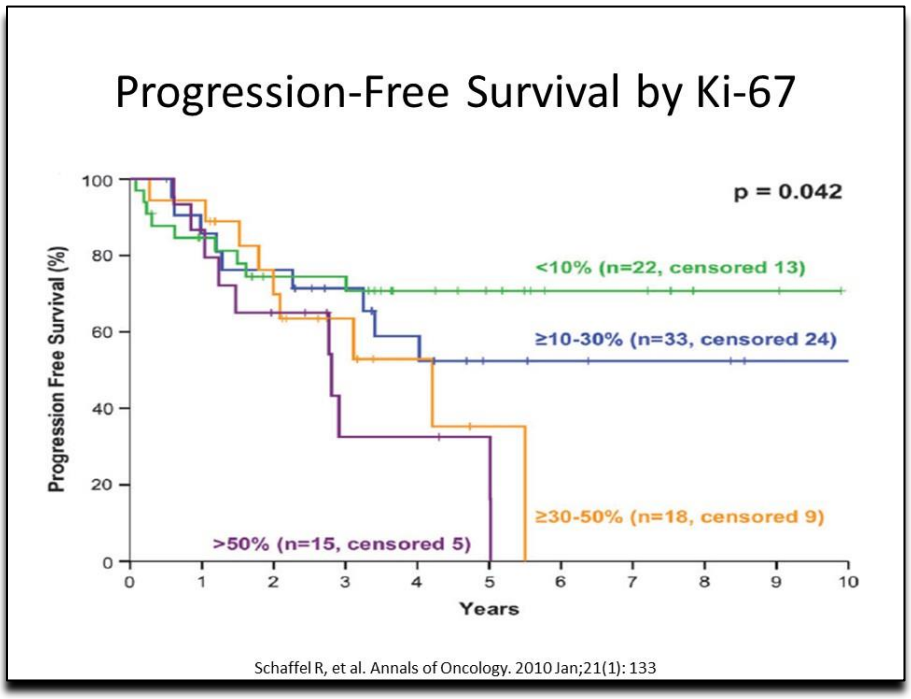
So, what about PETs, coming back to that? This is a neat study. It's very small. It was a total of about 36 individuals. But it did suggest that those who have very high PET signatures. And again, we look at this term SUV max—standardized uptick value is what that stands for—to say, "Hey, if you have a very, very bright lymph node or lymph nodes on a PET scan, do you do worse?"

And certainly, there was a hint of that. And in fact, I do look at PETs and look at the overall brightness. I don't use hard cutoffs, like this particular study did. It's important to remember that just as there have been improvements in care, there have also been improvements in how we do our PET CT imaging—how we deliver the PET/CT dye. There's a variety of things that can affect the magnitude of brightness. But it's a general sense of very high versus not very high.



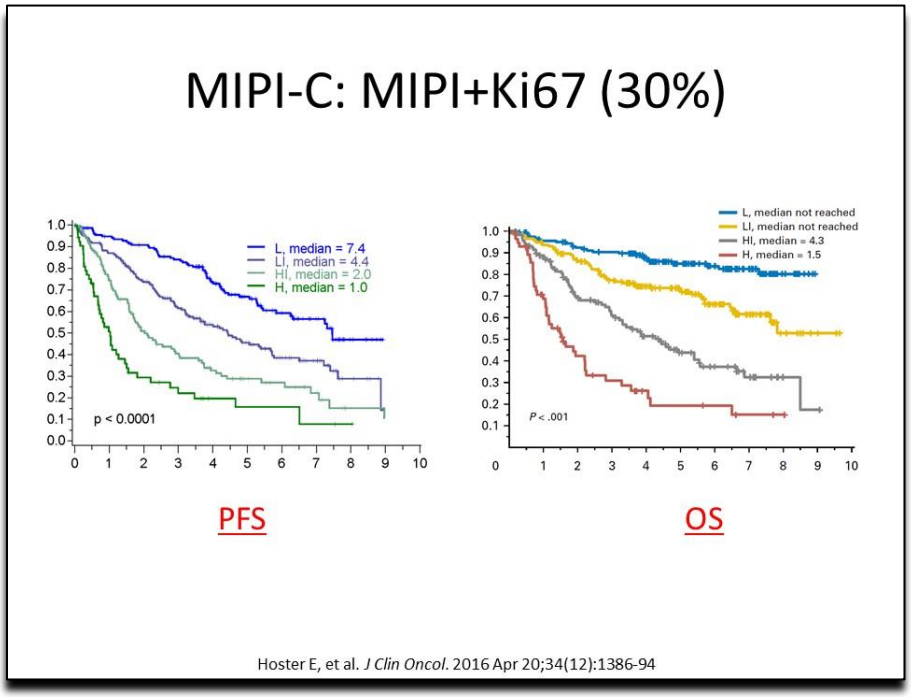
PET Uptake and Ki-67

And this may be one reason why. So, I told you that I was going to talk a little bit about what is a high growth rate and how do we measure that? There actually is a stain that we can use called the Ki-67. Some people also call it the MIB-1 index. And it's just a marker that stain cells that are committed to forming a copy of themselves. And you can see here that there's a pretty interesting correlation between just how bright that PET/CT is in those active involved lymph nodes and how high the growth rate is.



Progression-Free Survival by Ki-67

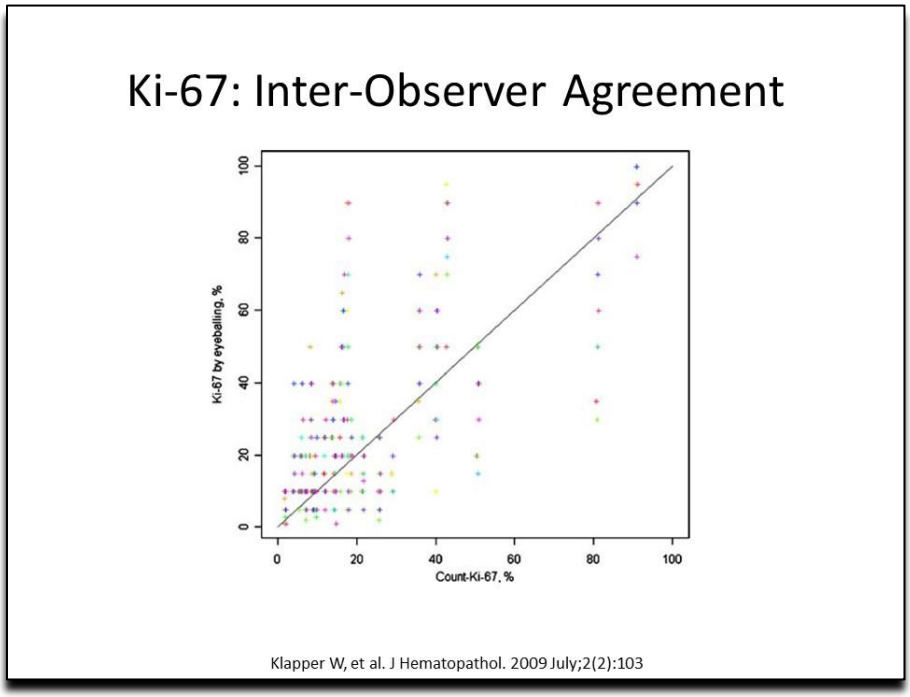
Digging a little bit more deeply into this Ki-67, this term progression-free survival means this is now looking at the proportion of people who are alive and in remission over time. And what you see is there's a cliff. We're doing fine if the growth rate is less than 10%. We're doing fine if it's 10% to 30%. But as we get over 30%, we fall off the cliff. Now all of a sudden, our expectations for that remission duration and that longevity drops quickly.



MIPI-C: MIPI+Ki67 (30%)

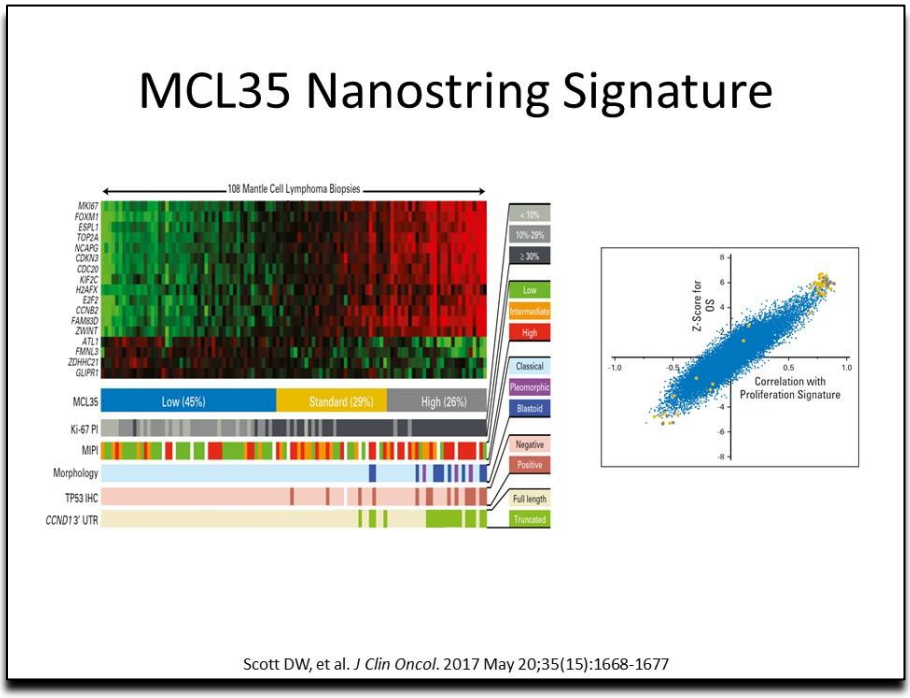
And so, the Germans built on this and developed a new MIPI score. They call it the MIPI-C. And here now for the first time, we can see the MIPI really performing well for not just overall survival but—that

same term, progression-free survival—that concept of what is the proportion of people who are not only alive but alive and in remission?



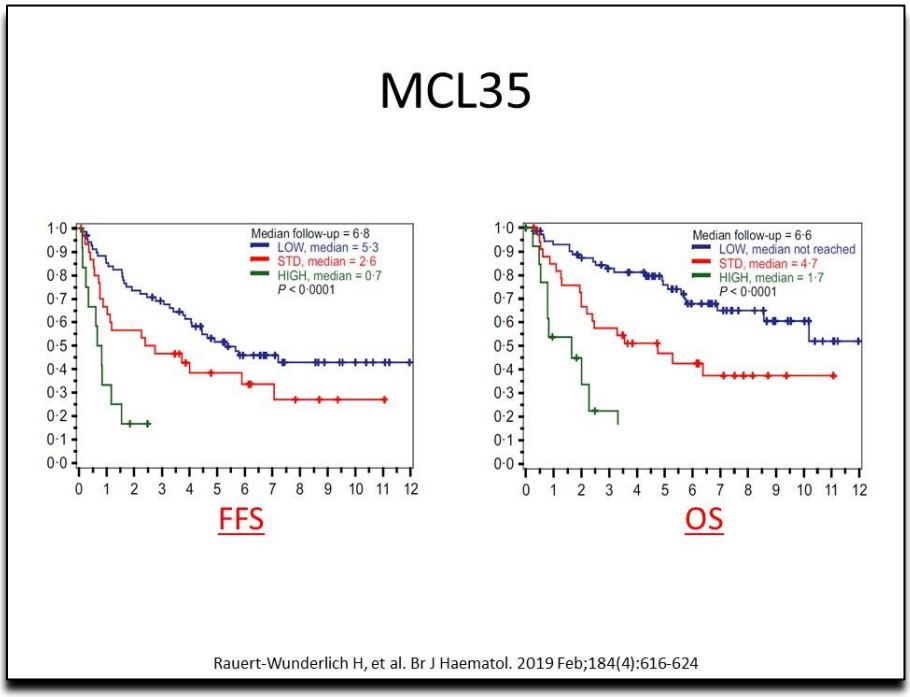
Ki-67: Inter-Observer Agreement

And you can see here very nicely that the growth rate seems to be a very important part of what we can expect with our chemotherapy. The problem is we really struggle to agree on the Ki-67 number, especially when we get close to around 30%, which again is that cliff. And so, this makes it a little bit challenging.



MCL35 Nanostring Signature

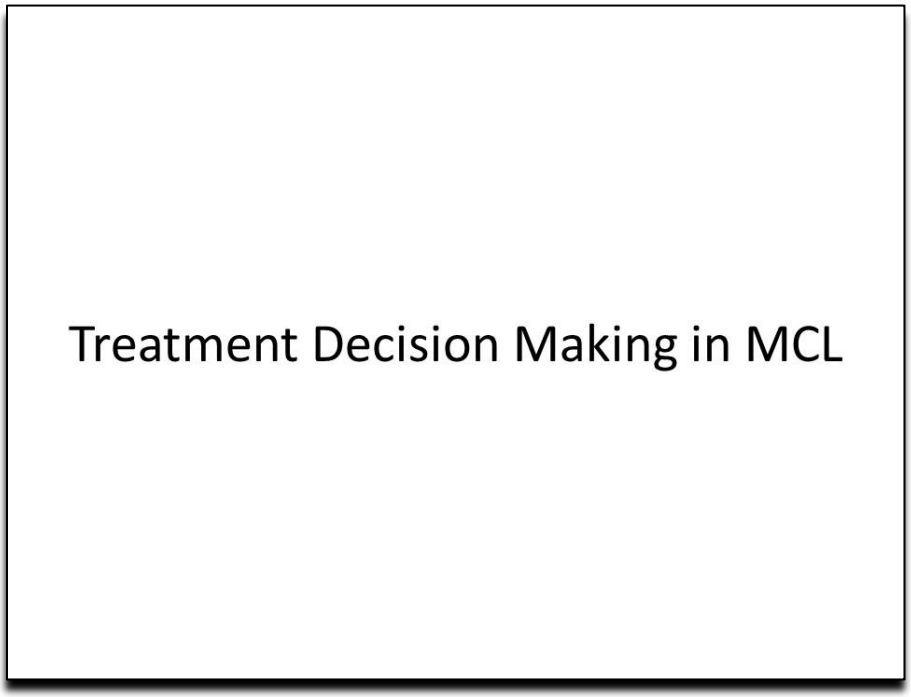
And so, the Europeans came up with a follow-up. They said, "Well, maybe we can do like the Spanish did" a few slides back and say, "Can we look at those genes that are being turned into proteins and come up with a score, a signature, that defines those patients that are growing more rapidly?" And that's exactly what they did with the MCL35 signature.



MCL35

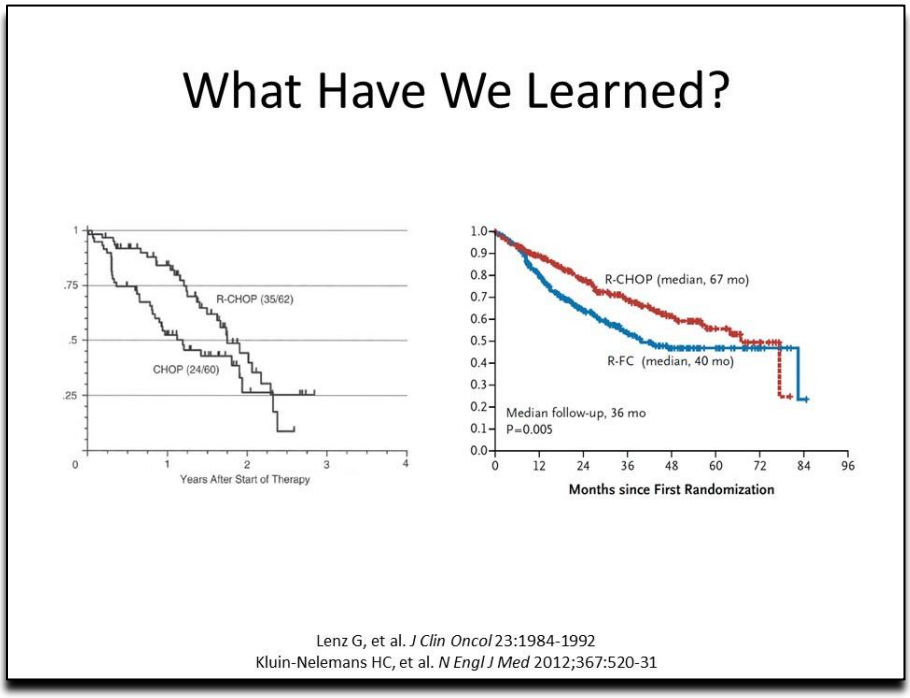
And you can see here that it was able to separate both and failure-free survival, or FFS—very similar to progression-free survival but able to discriminate length of remission—able to discriminate survival. And that is really cool because now again we have this tool that we can think about where we

don't have to worry so much about one pathologist agreeing with another pathologist on what the Ki-67 number is. This is going to give us a score—a hard-and-fast score—and one that we can run with.



Treatment Decision Making in MCL

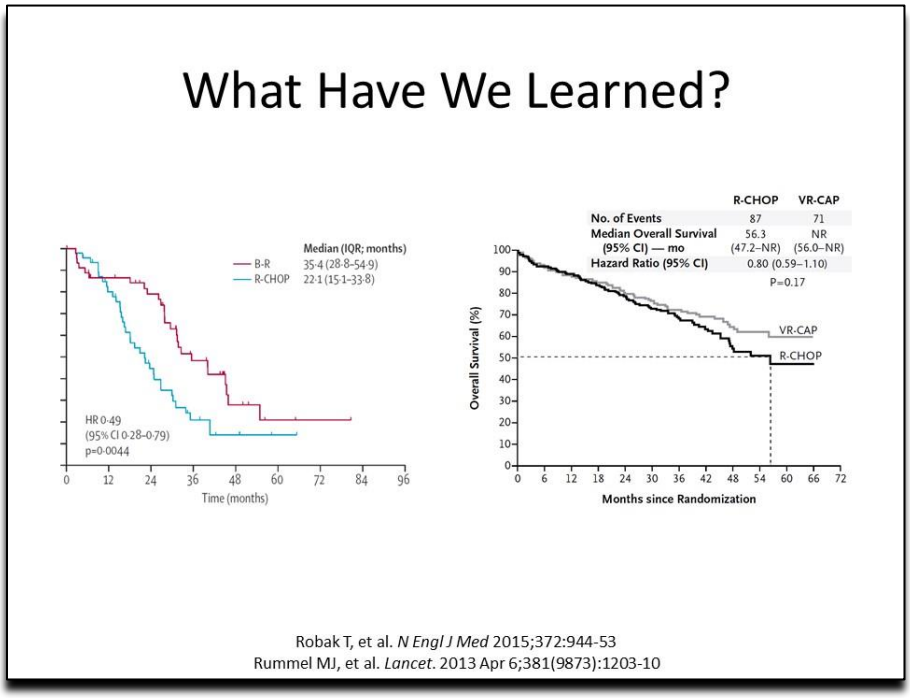
So, with all that in mind, how do we make treatment decisions? Now, we can predict how well someone will do based on these particular factors. But it still doesn't tell us what treatment to use or what treatment is optimal based on some of these factors.



What Have We Learned?

So, what have we learned? A couple of things. Adding rituximab (Rituxan®), an antibody therapy, to mantle cell lymphoma unequivocally improves outcomes.

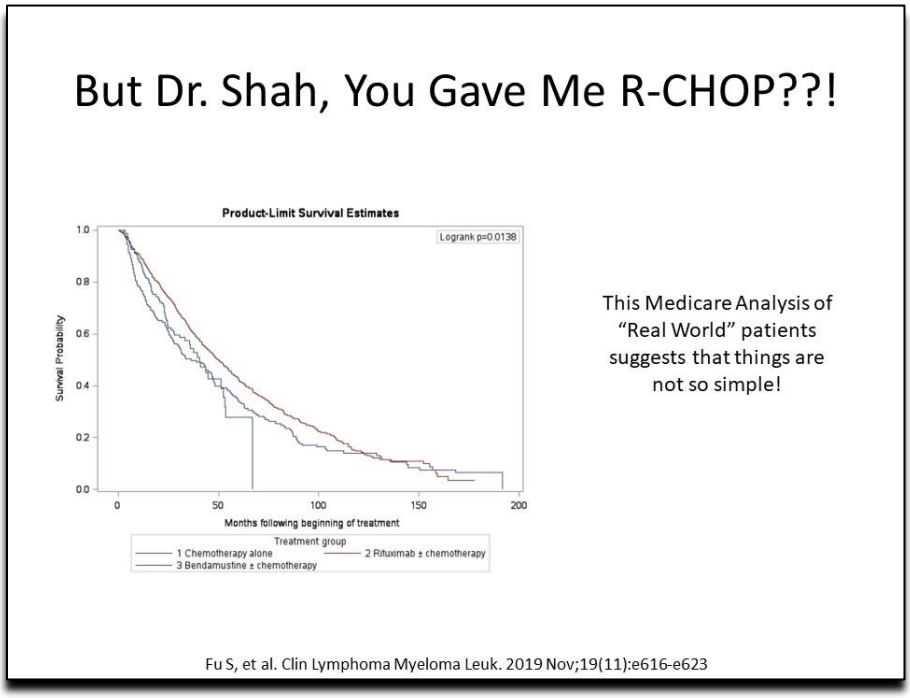
When we compare R-CHOP, and CHOP is just one of those standard regimens for mantle cell lymphoma. Very briefly, cyclophosphamide (Cytoxan®), hydroxydaunorubicin (doxorubicin) Oncovin® (vincristine), and prednisone. R-CHOP has become a standard of care—one of many—in mantle cell lymphoma. And here you can see that it was outperforming another regimen called FCR, which is fludarabine (Fludara®), cyclophosphamide (Cytoxan®), and Rituxan® (rituximab) in a randomized study. Why did it outperform fludarabine? Mainly because of toxicity. And you're going to hear me come back to this.



What Have We Learned?

So, have there been other comparisons? Yes. A more recent comparison using Velcade® or bortezomib in place of vincristine seemed to improve outcomes relative to R-CHOP. But we're not using a lot of Velcade® (bortezomib), and again the main reason being this concern about toxicity. Velcade® tends to come with neuropathy, numbness, tingling, or discomfort in the fingers and toes. That can be irreversible.

Now, I don't want to make it sound like it's occurring in the overwhelming majority of people. But when it occurs, it can be difficult to manage. And that has pushed a lot of us away from giving this particular regimen in spite of seeing that it was a little better than R-CHOP. Well, what about bendamustine? I will tell you now that bendamustine and rituximab is the most common therapy in the United States for newly diagnosed mantle cell lymphoma. And this particular comparison is one reason why.



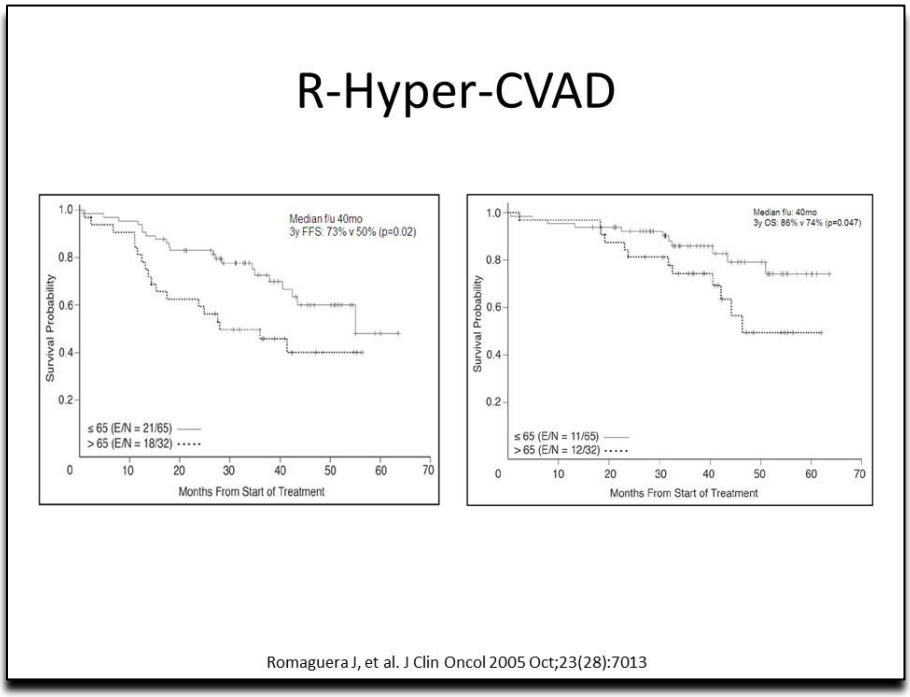
But Dr. Shah, You Gave Me R-CHOP??!

Now of course, I had to throw in the next slide, "But, Dr. Shah, I'm your patient, you gave me R-CHOP. What were you thinking?" And I always like to point out, in the real-world things are not so simple. This is a comparison of bendamustine; Rituxan®, with or without chemotherapy; and basically R-CHOP.

And you can see here the outcomes are essentially identical. So, why did one trial show a benefit where we're not seeing it on this Medicare population analysis? I'm going to go into that a little bit, but the bottom line is because mantle cell is wildly heterogeneous. And so, we're taking kind of a lot of factors as we're deciding what therapy we want to use up-front.

Defining Treatment Objectives: How Intensively Should We Treat?

So, one question that comes up next, "Well, if R-CHOP is not strong enough, can we push even harder, right?" We have more aggressive mantle cell. Can we just overcome that by treating more aggressively?

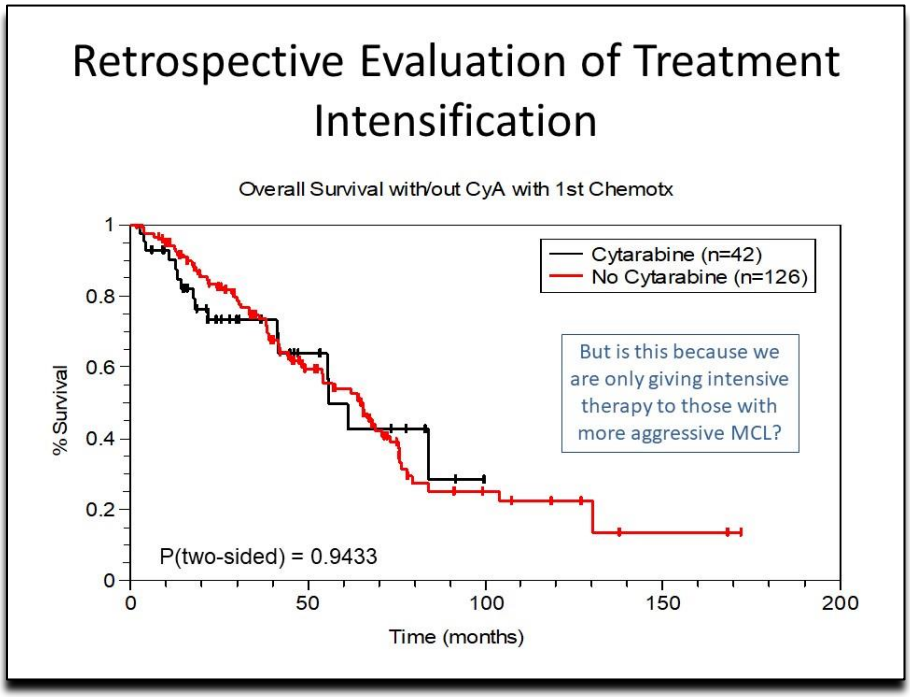


R-Hyper-CVAD

And really, one of the first hints we had with that was using this much more intensive protocol called R-hyper-CVAD. I won't go into the specifics, but I want to show these two curves because I think they're important.

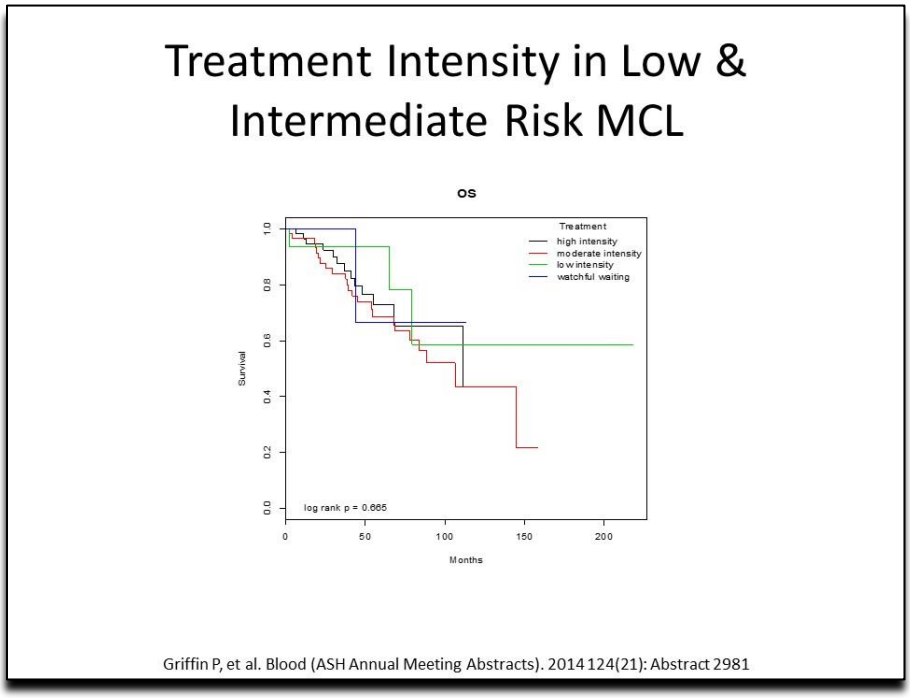
I told you in the beginning of the presentation that the median age was about 68. What we saw is, yes, we're treating younger individuals with hyper-CVAD. We're doing pretty well. We're not curing the mantle cell, but boy, we're out 5 years from diagnosis and a little over half of our patients are still in remission.

But look what's happening to those individuals that are 65 and older. One, we couldn't get as much of the hyper-CVAD in and, two, we weren't seeing the same benefit that we were seeing in our younger, fitter patients. And to that end, it's really made it hard to understand how we utilize this for those older individuals.



Retrospective Evaluation of Treatment Intensification

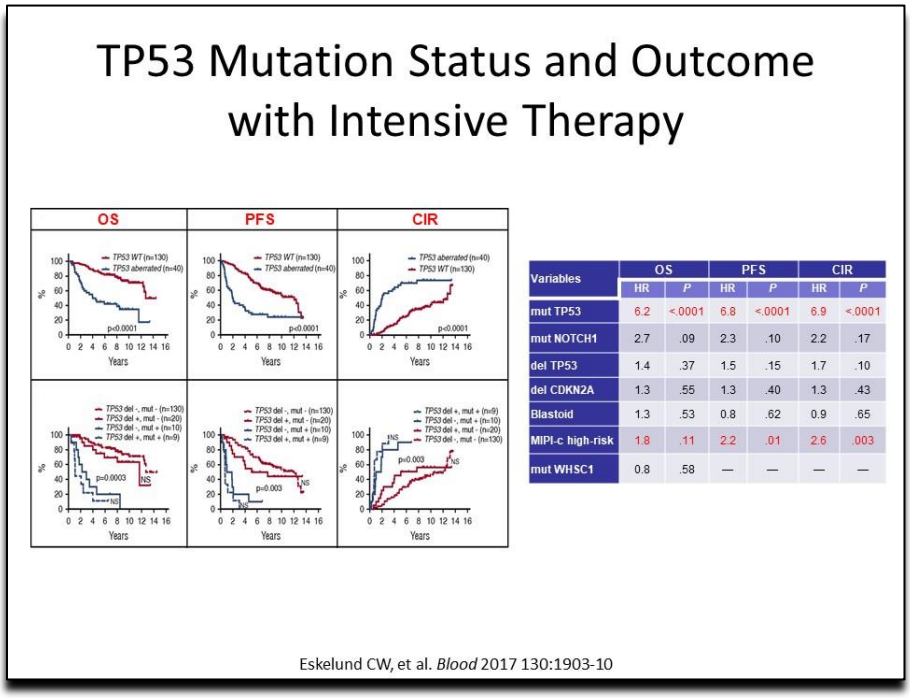
We wanted to go back and just say, "Hey, you know what?" And because that hyper-CVAD regimen, one of the key elements is including high-dose cytarabine , we wanted to ask, "Does that matter?" And so, we just did just an on-the-spot analysis to say, "Hey, which patients got cytarabine and which patients didn't?" Because really, they were only getting this hyper-CVAD regimen. So really, it's hyper-CVAD versus all of our other therapies. And we said, "Does it matter?" And the answer is, "No." Folks had the same survival expectation.



Treatment Intensity in Low & Intermediate Risk MCL

But you could make a very simple argument because this isn't what we call a prospective trial where we enroll people and we flip a coin, and we randomize one way or the other. This is, "Hey, you're getting treatment. This is the treatment you got." We don't know what the decision-making was at the time, and it could be that only those who had more aggressive mantle cell lymphoma—the ones who were also already predicted to do worse—are the ones getting the more intensive chemotherapy.

And so, you could say that, "Hey, if anything, maybe you improved outcomes for that group of patients because now they're doing as well as all the low-risk patients." So, we wanted to answer exactly that question. The bottom line is we looked now only at those patients with low- and intermediate-risk mantle cell lymphoma, and we couldn't show any benefit with intensifying their therapy using regimens like hyper-CVAD.

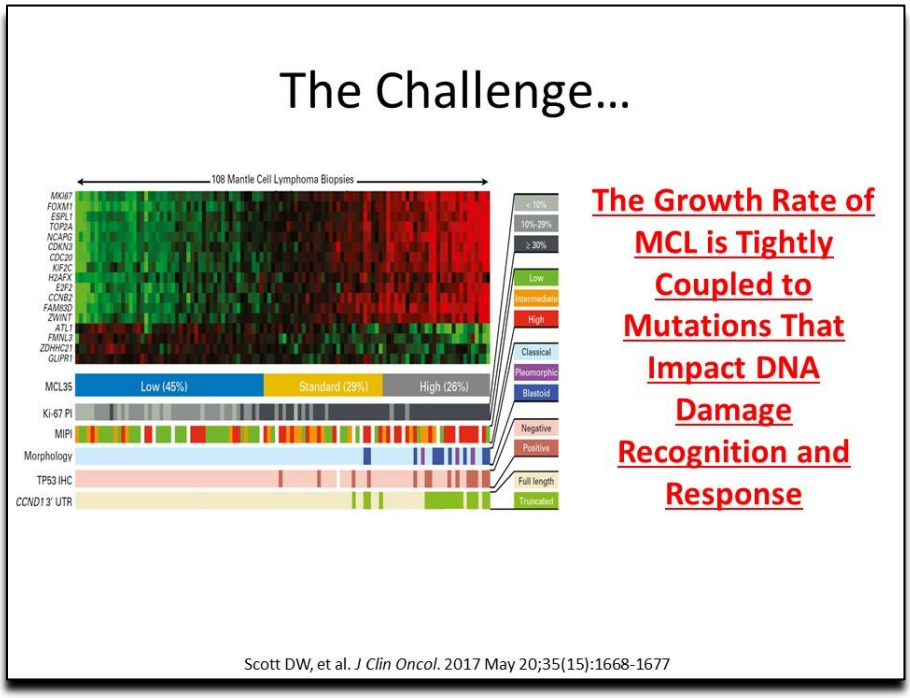


Variables	OS		PFS		CIR	
	HR	*P*	HR	*P*	HR	*P*
mut TP53	6.2	<.0001	6.8	<.0001	6.9	<.0001
mut NOTCH1	2.7	.09	2.3	.10	2.2	.17
del TP53	1.4	.37	1.5	.15	1.7	.10
del CDKN2A	1.3	.55	1.3	.40	1.3	.43
Blastoid	1.3	.53	0.8	.62	0.9	.65
MIPI-c high-risk	1.8	.11	2.2	.01	2.6	.003
mut WHSC1	0.8	.58	—	—	—	—

TP53 Mutation Status and Outcome with Intensive Therapy

This may be one really important reason why. This is simply saying that if you have a mutation in that TP53—that same one I talked to you about before—that controls to some degree chemotherapy sensitivity, if you have that mutation, you don't do as well, even when you get extraordinarily intensive chemotherapy.

So, now we can say: "You know what? It doesn't really benefit the low- and intermediate-risk patients because they're going to do well no matter what we do. And for the very high-risk patients, particularly those who had these mutations, it's not really clearly going to benefit them either. So then, what are we doing?"

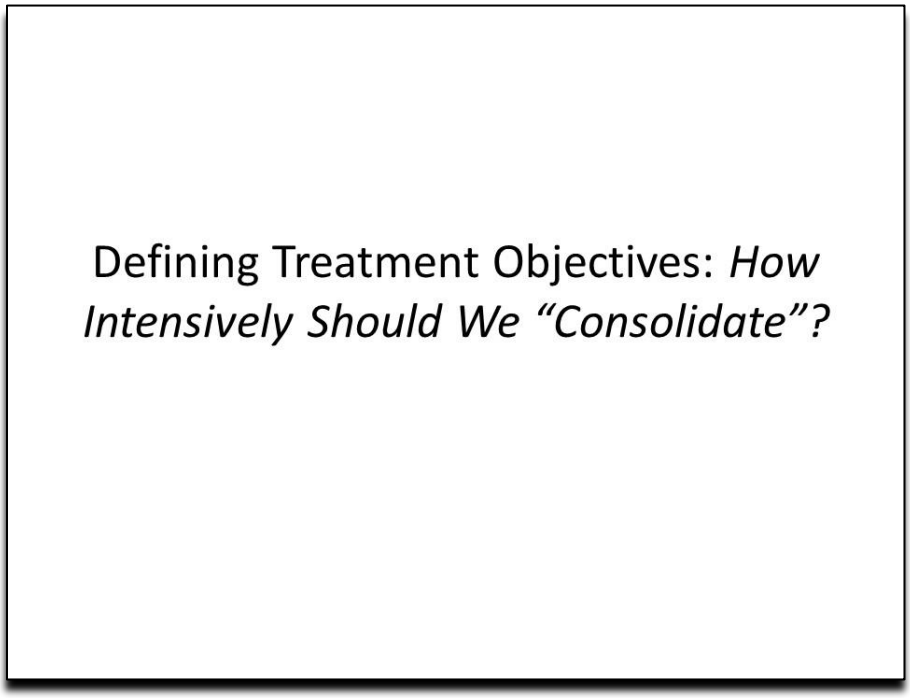


The Challenge…

And this is the part of the figure that I glossed over. And if you look at the bottom, we're now saying, how many patients have a Ki-67 over 30%? That's the dark gray. How many have a high MIPI?

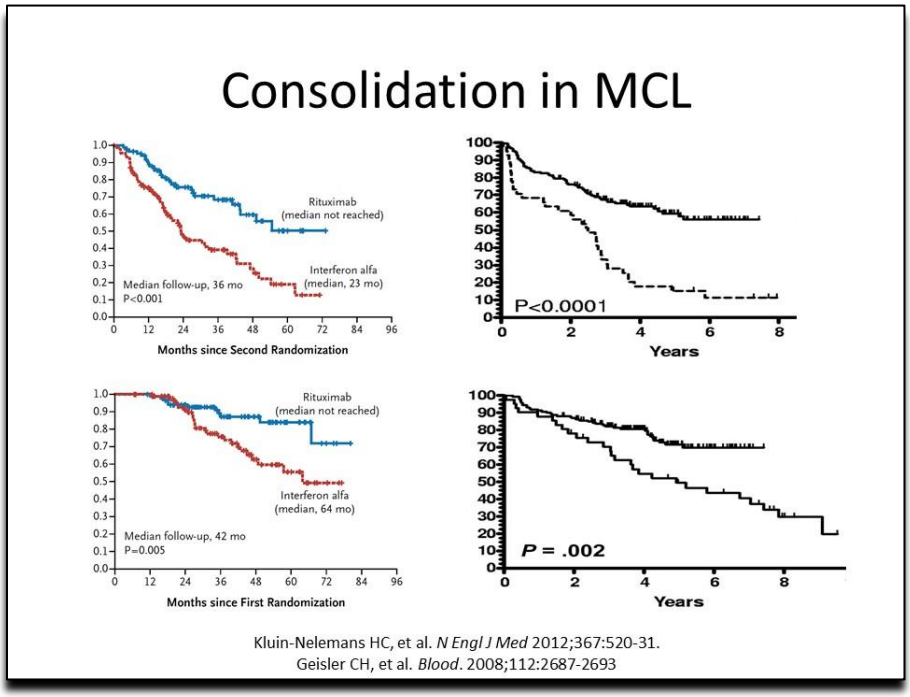
That's the red. How many have blastoid or pleomorphic mantle cell? That's the blue and purple. How many have TP53 mutations? That's the dark pink.

And then there's this other cyclin D1 mutation that I won't go into. But the bottom line is the faster mantle cell grows—or the more fastly growing mantle cell lymphomas, I should say—tend to have mutations that affect the cells' ability to grow and divide. And on a certain level, it kind of makes sense, right? Mantle cell lymphoma, in order to grow and divide, has to be able to ignore DNA damage.



Defining Treatment Objectives: How Intensively Should We "Consolidate"?

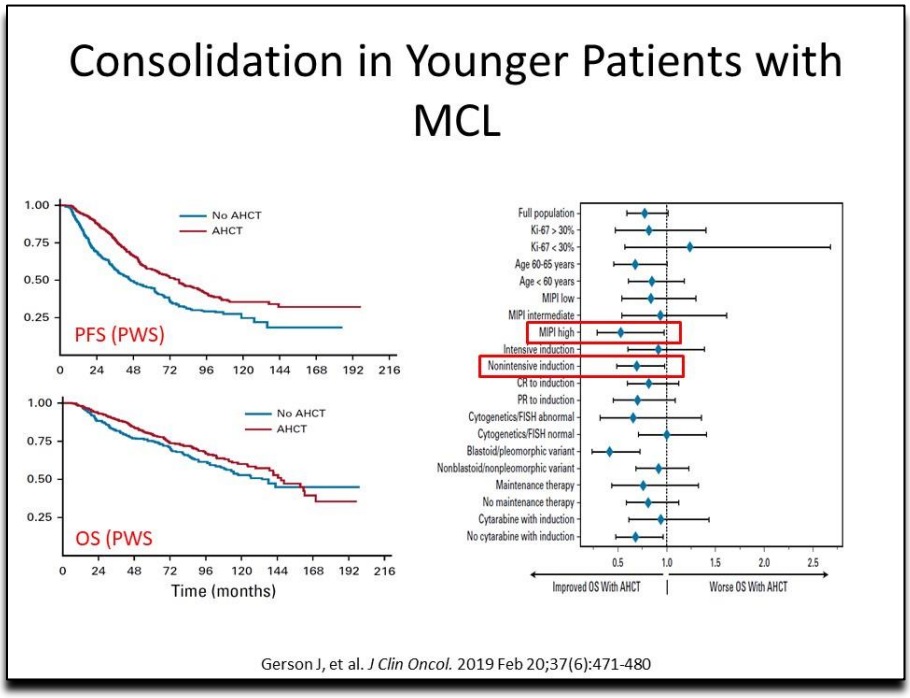
How intensively should we treat after someone is in remission?



Consolidation in MCL

This is a really cool trial on the left that gave rituximab maintenance after an R-CHOP chemotherapy. And they certainly show that giving rituximab improved outcomes. But what I put on the right that I didn't label is a similar trial where folks got more intensive chemo and a stem cell transplant.

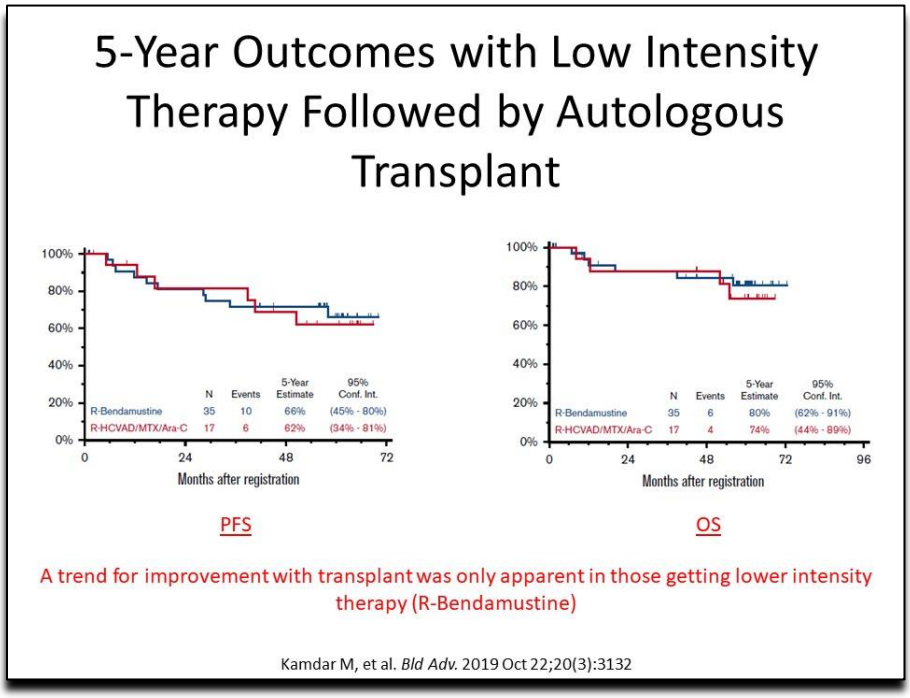
And what I simply want to highlight is when we talk about the top, which is how long they're in remission, and when we talk about the bottom, which is how long they're alive, you can't really tell there's much difference. Whether we gave Rituxan® as a maintenance or whether we gave a stem cell transplant. Whether we gave R-CHOP as our front-line therapy or whether we gave something called maxi-CHOP, which is, again, that more intensive protocol.



Consolidation in Younger Patients with MCL

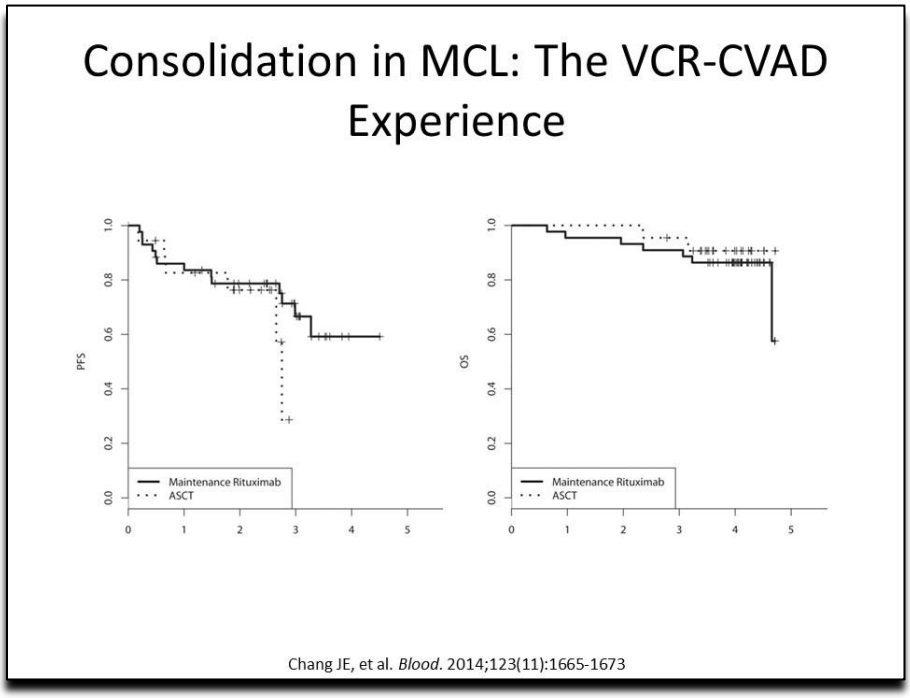
And so, what it tells me is, "Hey, we can achieve really good outcomes by focusing on maintenance rather than intensity." We could show similar things when we try to just look broadly to say, "Hey, how much does a transplant benefit folks?" And you can see there's a little bit of a benefit in how long people are in remission but no benefit in survival.

So, there were some things that fell out. One of those was from the very high-risk patients. Maybe there was some benefit. Again, I say, "Maybe." You saw the data I presented earlier. But here's where I think the real key is. If they're not getting very intensive chemotherapy up-front, then the transplant may help make up for that, particularly in those higher-risk individuals.



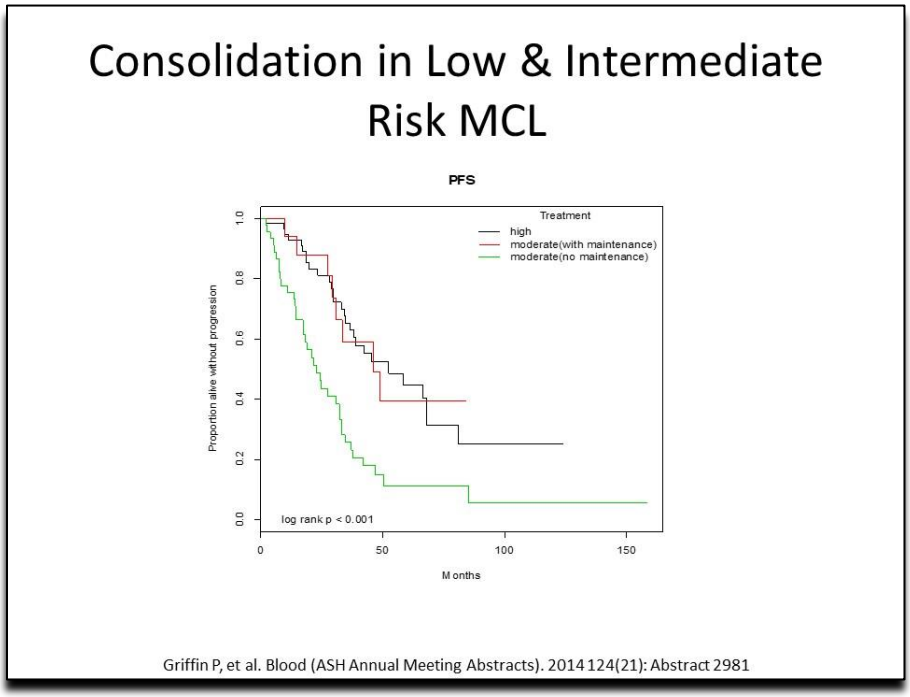
5-Year Outcomes with Low Intensity Therapy Followed by Autologous Transplant

This is another trial, just saying, “Hey, you know what, if we gave a low-intensity regimen, this was bendamustine and Rituxan® as opposed to that hyper-CVAD, the one that had the cytarabine in it.” How do folks do when you can see here they did very similar in terms of their remission and their survival? But what the key here is noting that many of the patients who got the more intensive chemotherapy did not go to transplant, and many of those who got bendamustine did.



Consolidation in MCL: The VCR-CVAD Experience

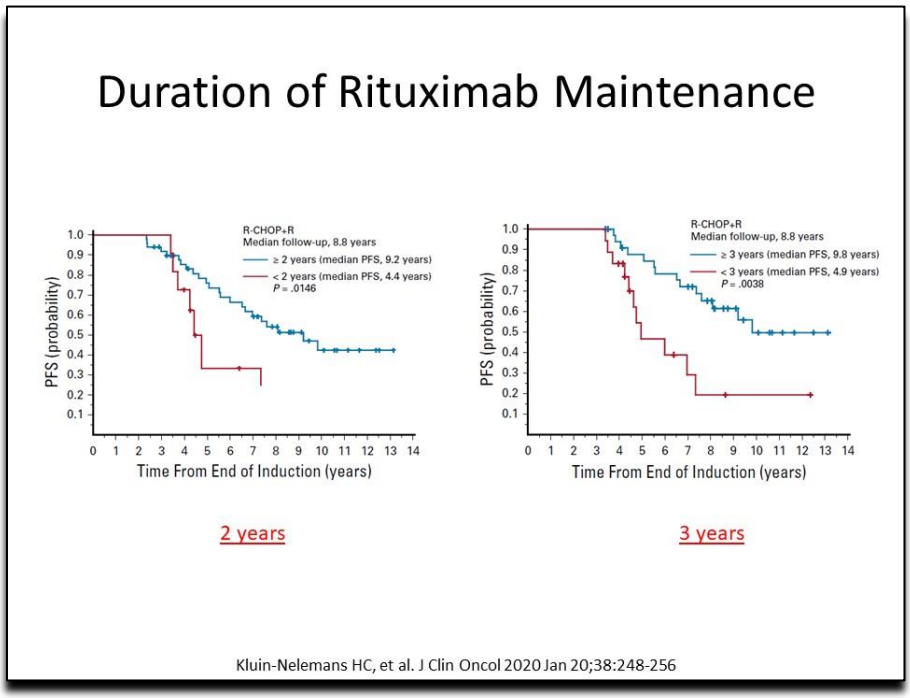
And in particular, for those who got bendamustine—so, low-intensity therapy up-front and then got a transplant. Now we're seeing survival that mimics what we would get from more intensive chemotherapy, and that's important. There have been attempts to bridge the two—that is, giving intensive chemotherapy and Rituxan® maintenance. And again, when we do that we can see that the outcomes are at least as good as giving that same intensive chemotherapy in transplants.



Consolidation in Low & Intermediate Risk MCL

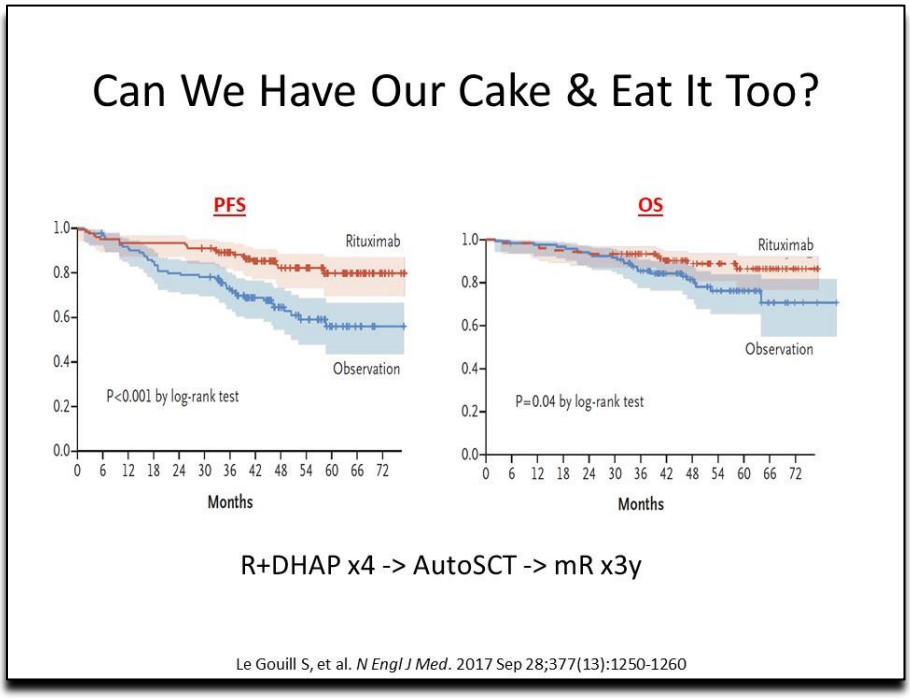
When we looked at our own outcomes again, we simply asked, "Intensive chemotherapy or less intensive with maintenance?" And now we could see no difference in outcome in our low- and

intermediate-risk mantle cell lymphoma patients. Now where we did see poorer outcomes is if we did a low-intensity approach and no maintenance rituximab. We just gave the low-intensity chemo and stopped.



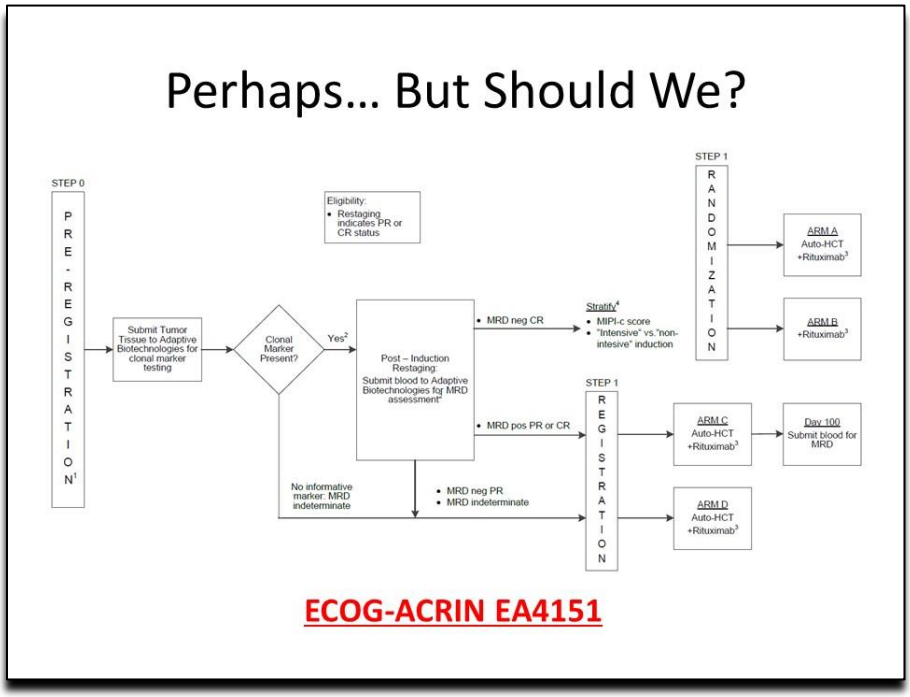
Duration of Rituximab Maintenance

What about the duration of maintenance Rituxan®? Again, this looked at folks who got 2 years or more or 3 years or more of maintenance Rituxan®. And the bottom line is, the longer we gave it the longer people were in remission.



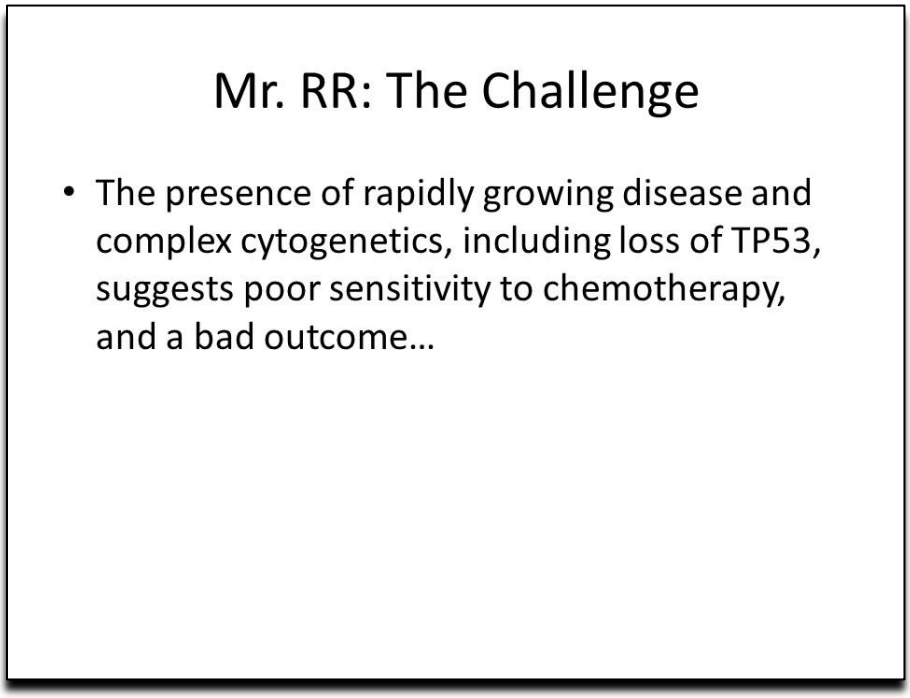
Can We Have Our Cake & Eat It Too?

But can we have our cake and eat it, too? The answer is we can. This is a study that gave high-dose chemo using cytarabine—that's what the "A" in this DHAP is—stem cell transplant, and then 3 years of maintenance Rituxan®. And you can see here the folks who got Rituxan® did much better than those who didn't.



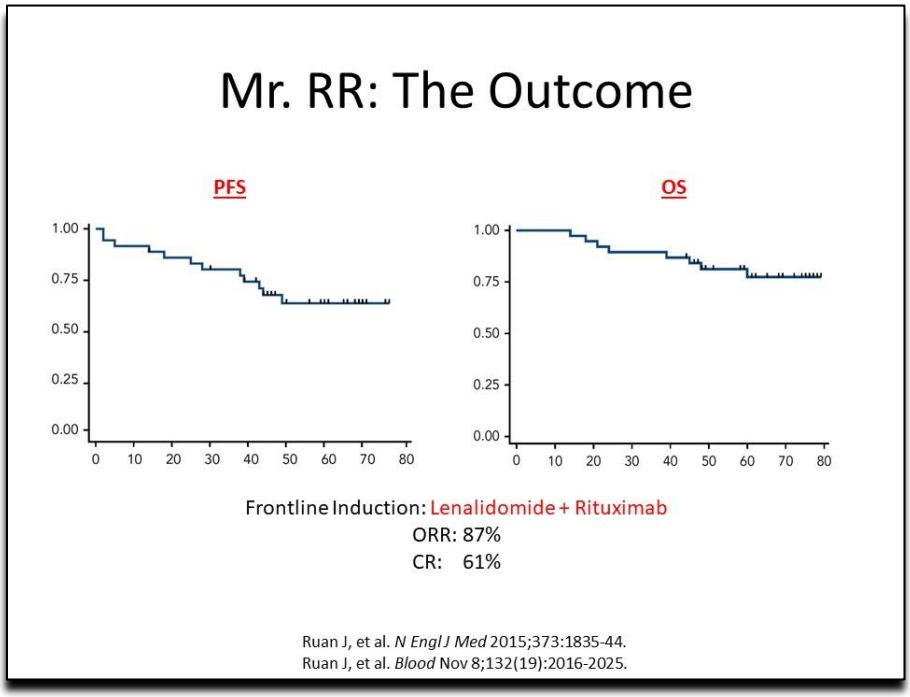
Perhaps... But Should We?

But should we? That's a lot of therapy. That's a lot of intensity. And I think it's a question that's unresolved and one we hope to resolve on this particular clinical trial. This is a randomized study asking, "Shall we do stem cell transplant and rituximab or just rituximab alone?"



Mr. RR: The Challenge

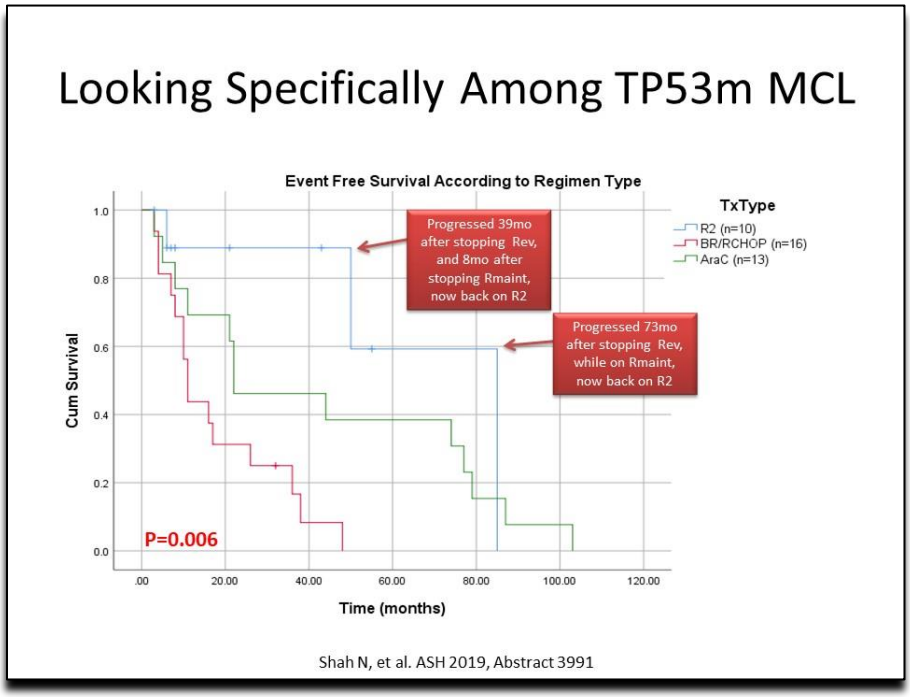
So, the challenge again in treating Mr. RR is he's got rapidly growing disease, he has that TP53 mutation. So, what are we doing to do because high-dose chemo is probably not going to do well, and he's now in his mid- to late-60s? We're also going to have trouble getting the chemo in him and have it be tolerable.



Mr. RR: The Outcome

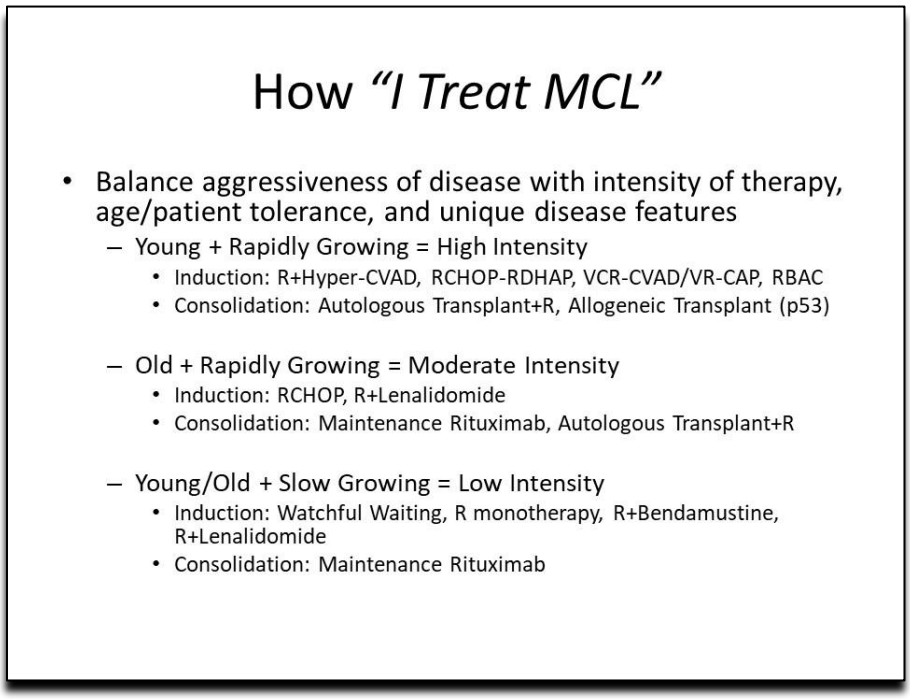
So, what we did is we enrolled him on this trial of Revlimid® (lenalidomide) and rituximab, or lenalidomide and rituximab. And lenalidomide is an immune therapy. Think of it as something that activates the immune system and helps to better respond to the rituximab. It has other

things that it does as well. But the bottom line is we saw outcomes that paralleled what we saw with more intensive chemotherapy, and he was enrolled in this trial and did very, very well.



Looking Specifically Among TP53m MCL

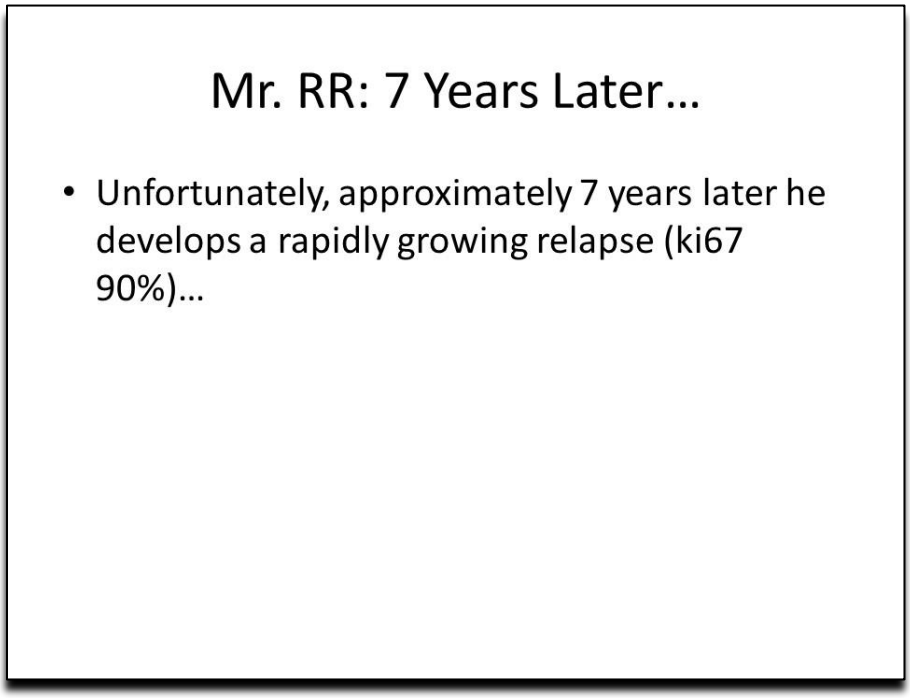
If we look specifically at our own experience in TP53-mutant mantle cell lymphoma, these are small numbers. But again, we could show that folks who are getting Revlimid® and rituximab do at least as well as those who are getting more intensive or less intensive chemotherapy approaches.



How "I Treat MCL"

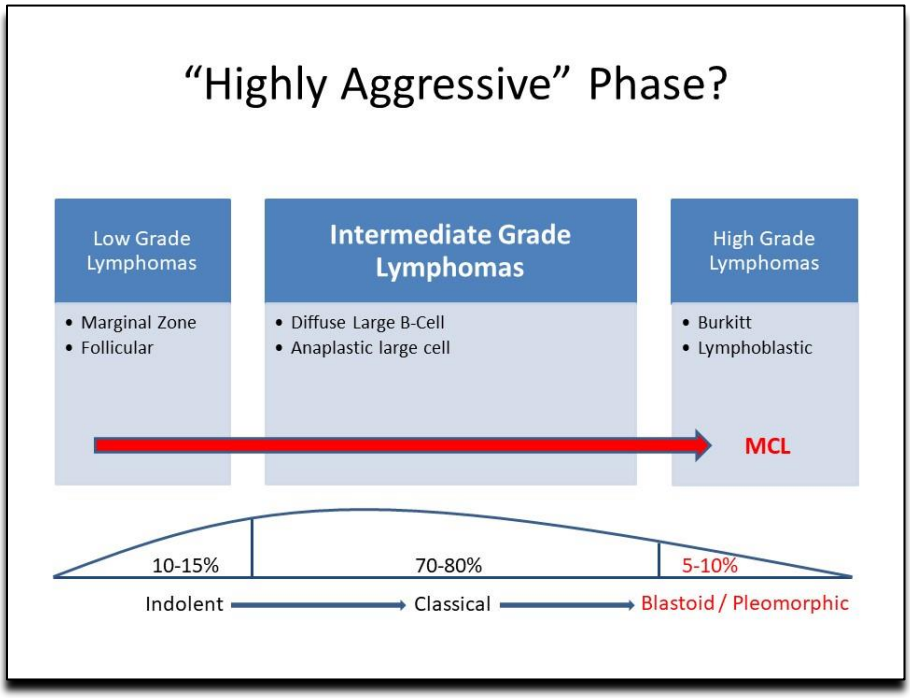
So, how do I treat mantle cell lymphoma? For the young with rapidly growing disease, yes, I still consider hyper-CVAD. Yes, I still consider intensified regimens because I'm trying to get their disease under control. And they're young, and I think they can tolerate it. For those that have those p53s, rather than using autologous transplant, which is using your own stem cells, I try to lean towards an allogeneic transplant—one that uses somebody else's stem cells to try and hopefully better manage their disease and keep it from coming back.

For those who are older who have rapidly growing disease, we're not going to achieve the same benefit. And now I'm leaning more on less intensive approaches but really, really trying to think about what I do with my maintenance rituximab, really trying to figure out how to get that going. And again, we struggle here in terms of those with rapidly growing disease who are older. For those who are young or old with slower growing disease, we try to watch them. If they do need therapy, then again, we're going to lean towards less intensive approaches—again, building on maintenance rituximab.



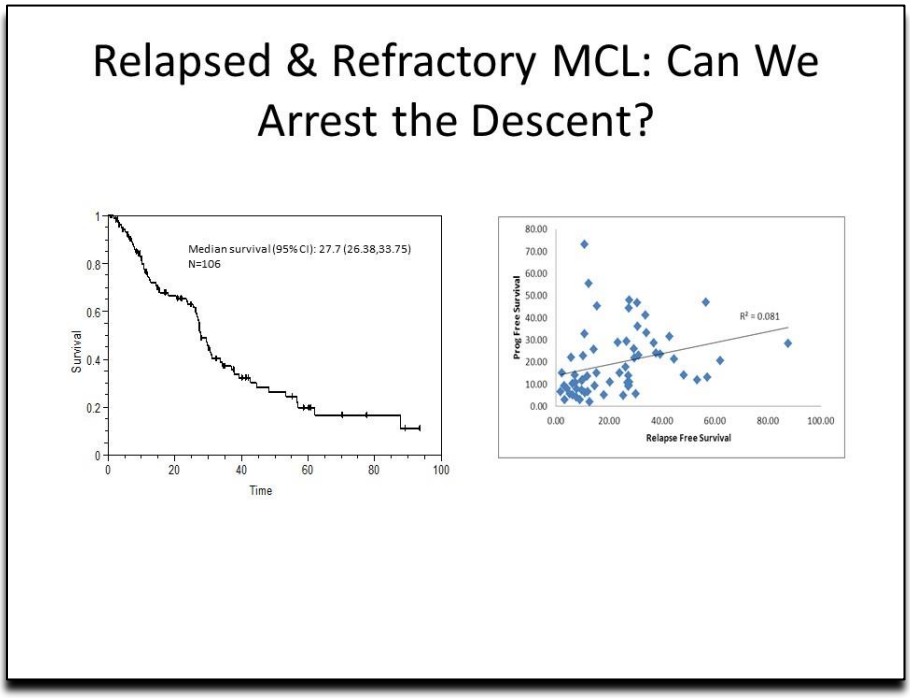
Mr. RR: 7 Years Later…

So, unfortunately, Mr. RR did develop a relapse about 7 years later, and his Ki-67 was very high.



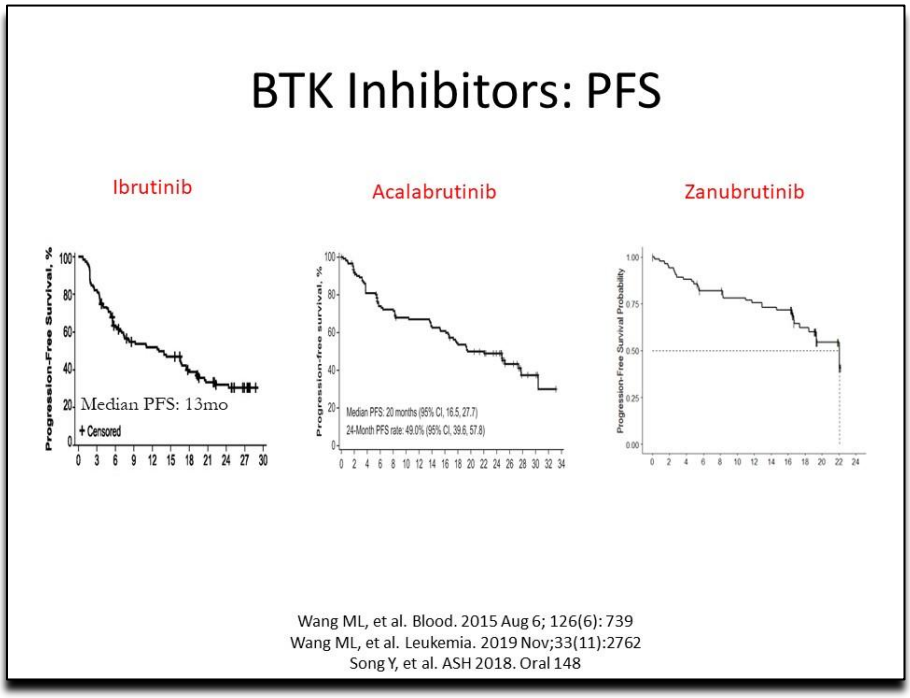
"Highly Aggressive" Phase?

He is now in this high-grade category.



Relapsed & Refractory MCL: Can We Arrest the Descent?

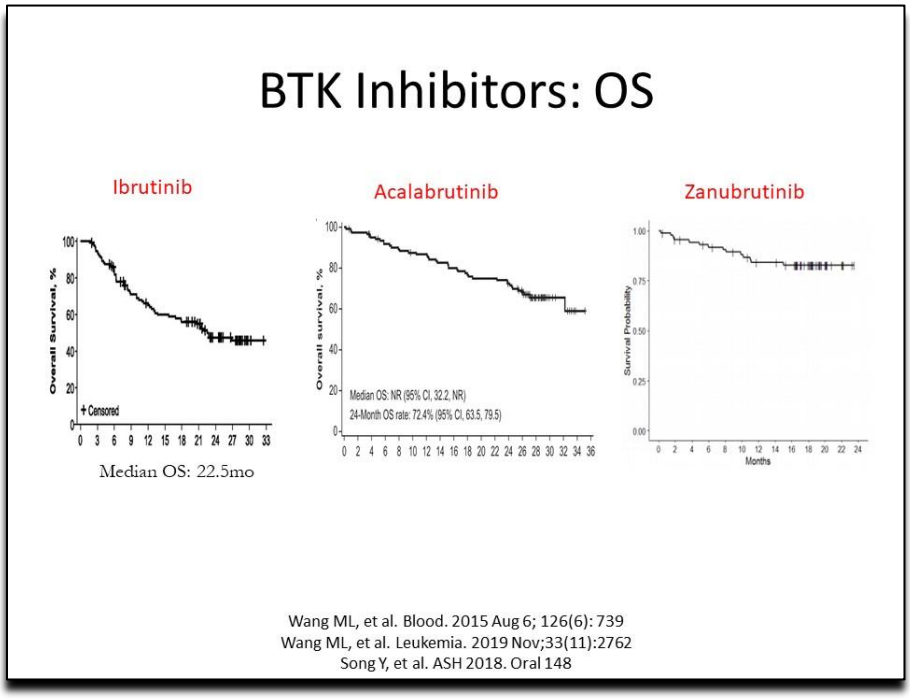
And so the question is, "What do we do?" We know that once we get to this point that we're in trouble.



BTK Inhibitors: PFS

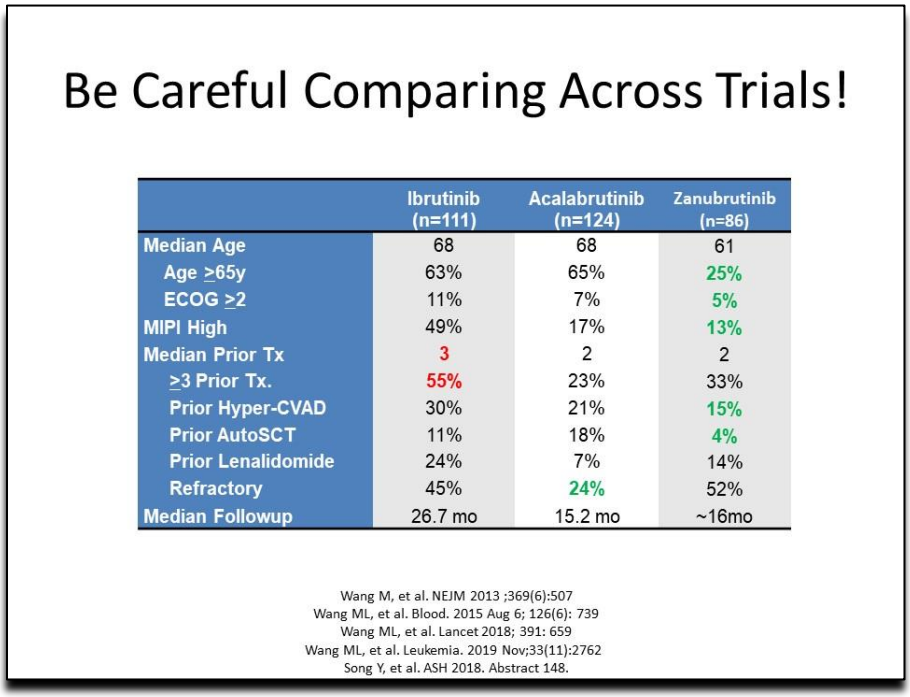
And so, talking a little bit about BTK inhibitors, since I know that's a major interest from a lot of folks. The first thing I want to point out is the progression-free survival is similar for all three of the BTKs, okay? They have a similar progression-free survival. The reason the curve is a little different is the amount of time that they were watched is a little different and what state they were in when they came

onto the trial—meaning were they early in their history of mantle cell or later—seemed to really affect how these curves look.



BTK Inhibitors: OS

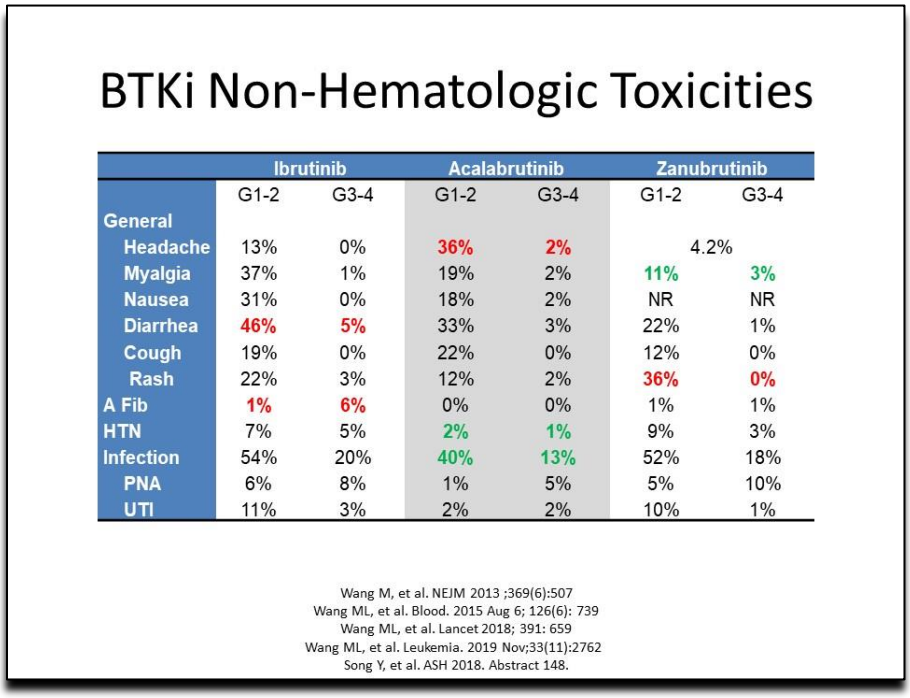
Again, overall survival is also very, very similar.



	Ibrutinib (n=111)	Acalabrutinib (n=124)	Zanubrutinib (n=86)
Median Age	68	68	61
Age ≥65y	63%	65%	25%
ECOG ≥2	11%	7%	5%
MIPI High	49%	17%	13%
Median Prior Tx	3	2	2
≥3 Prior Tx.	55%	23%	33%
Prior Hyper-CVAD	30%	21%	15%
Prior AutoSCT	11%	18%	4%
Prior Lenalidomide	24%	7%	14%
Refractory	45%	24%	52%
Median Followup	26.7 mo	15.2 mo	~16mo

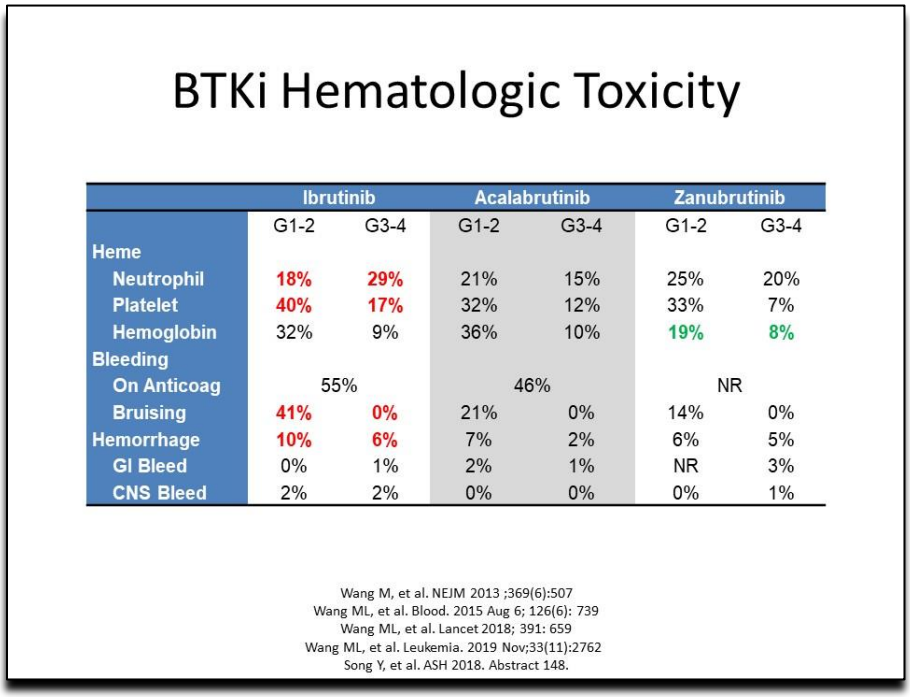
Be Careful Comparing Across Trials!

And so, this is again just highlighting that there are major differences in the types of patients who came onto these particular trials.



BTKi Non-Hematologic Toxicities

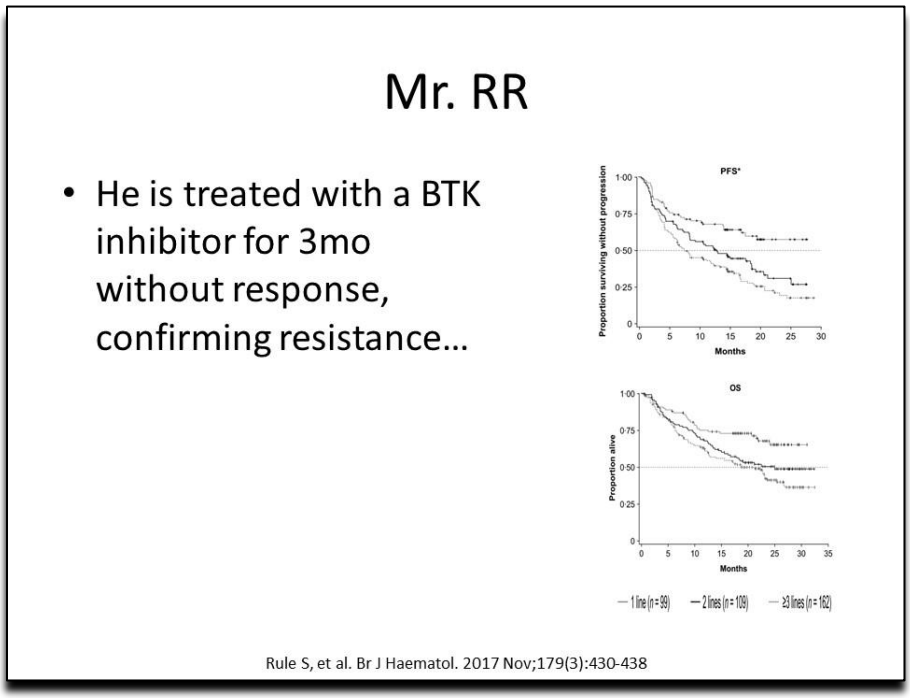
So then, how do we decide between the three? The answer is side effects, side effects, side effects. We take our patient, and we say, "If you already have a history of heart disease, do we really want to go towards ibrutinib?" Probably not. We'll lean towards acalabrutinib (Calquence®) or zanubrutinib (Brukinsa™).



BTKi Hematologic Toxicity

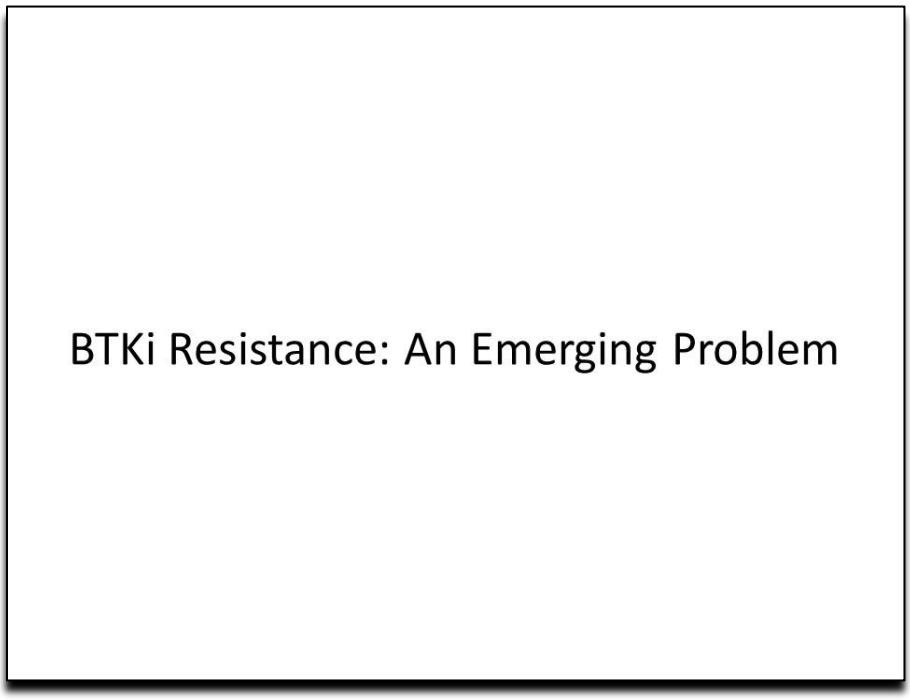
For people who require a proton-pump inhibitor, we may lean a little bit more towards zanubrutinib, where we've seen that the drug is still safely absorbed. We are going to still see some toxicities that

are unique. Zanubrutinib tends to have a little bit more in the way of low neutrophils relative to the other two. We can also see more rash with zanubrutinib, and with acalabrutinib more muscle aches and headaches.



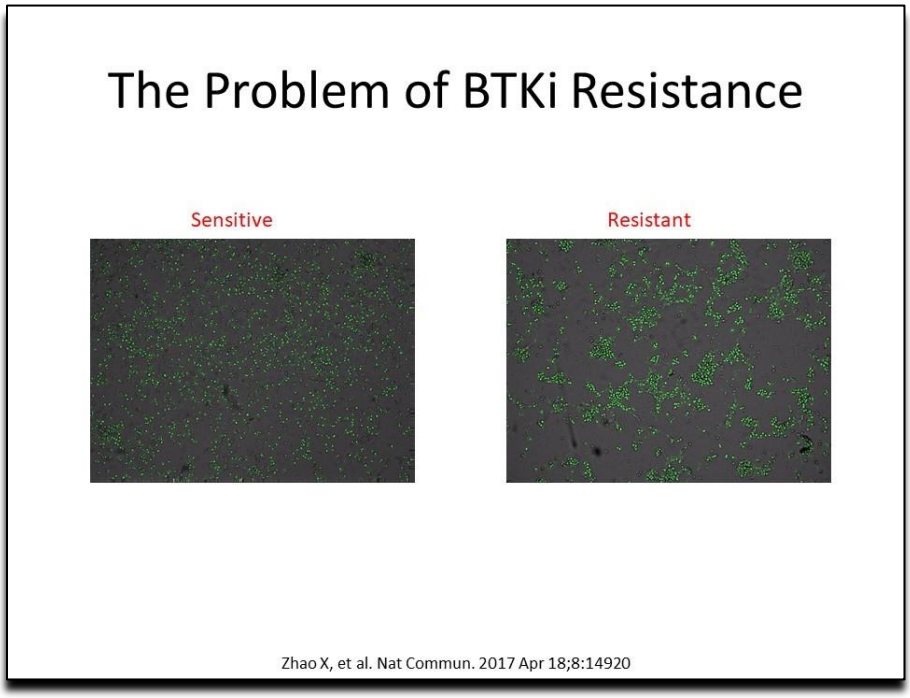
Mr. RR

So, he received this BTK inhibitor, and what you'll see here is the PFS and overall survival curves by line of therapy. And so, the problem is the later we use the BTK inhibitor the less well it works.



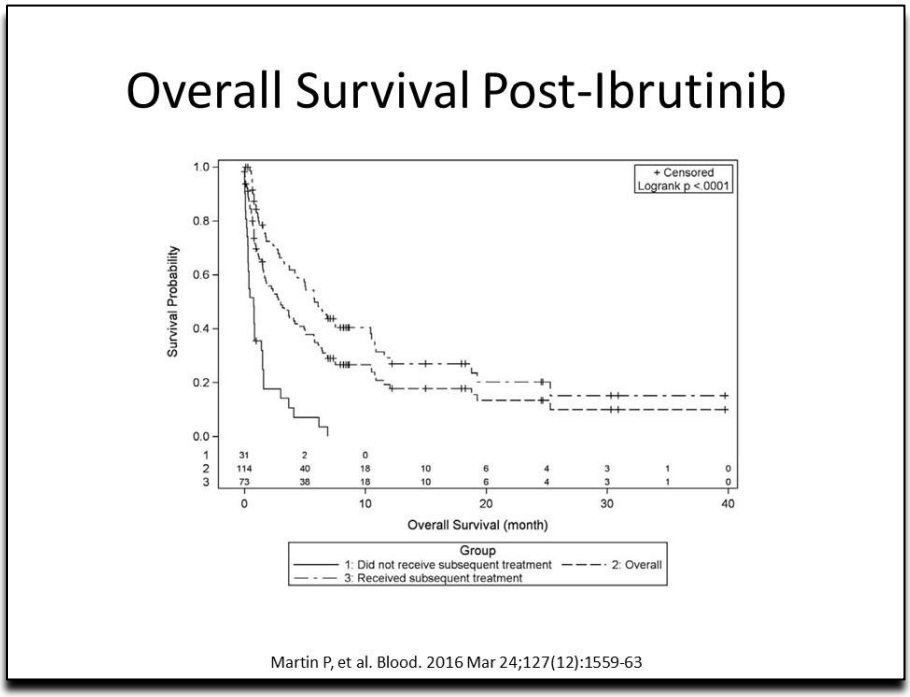
BTKi Resistance: An Emerging Problem

And so, BTK resistance is a big problem.



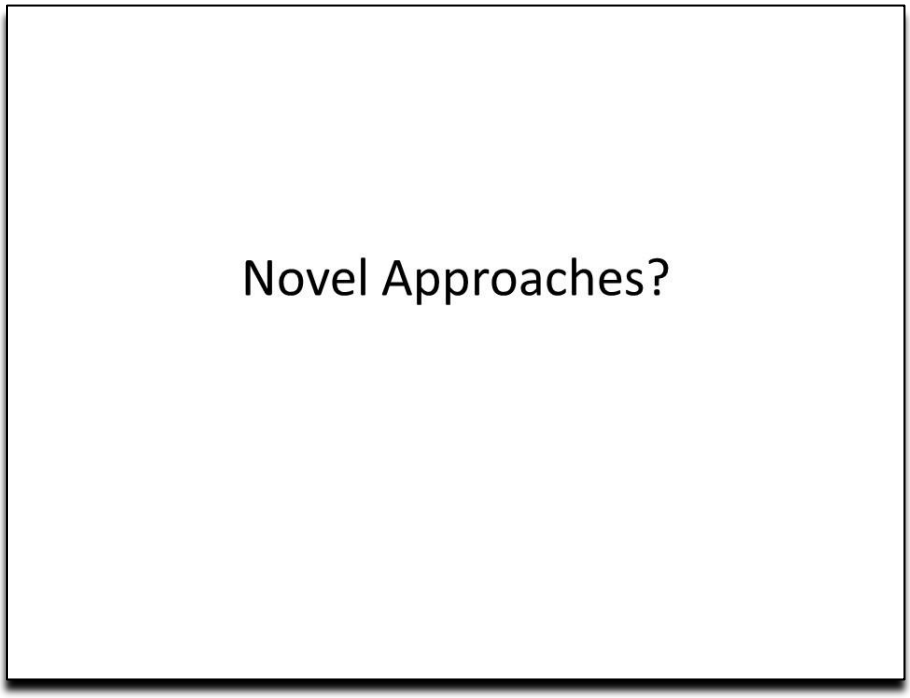
The Problem of BTKi Resistance

I'm just showing that when it emerges, again.



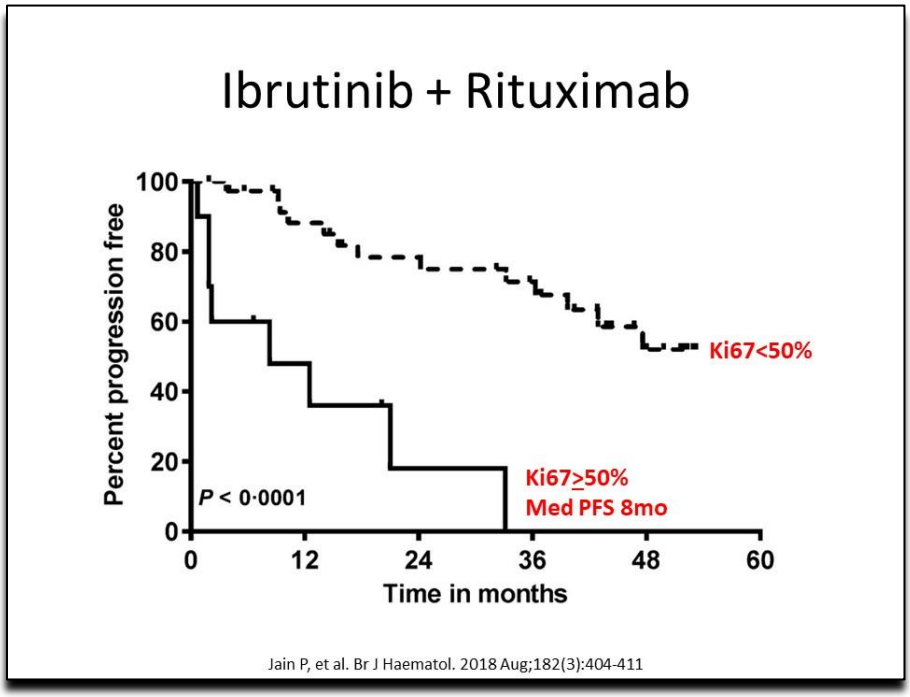
Overall Survival Post-Ibrutinib

These are people who are late on the disease course, but the outcomes are very poor. It's very hard to get these patients back into remission.



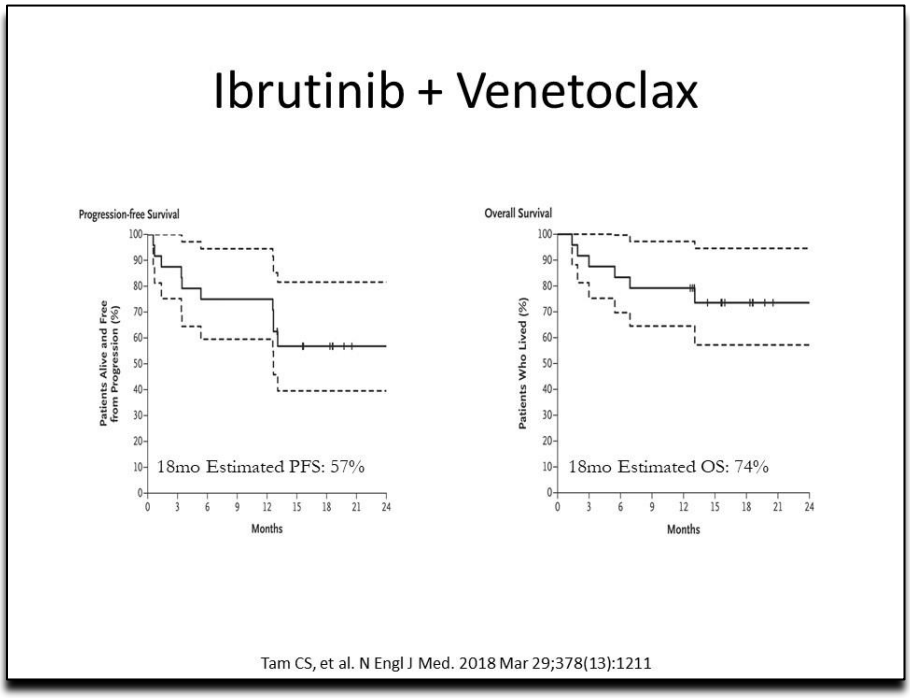
Novel Approaches?

So, we need novel approaches.



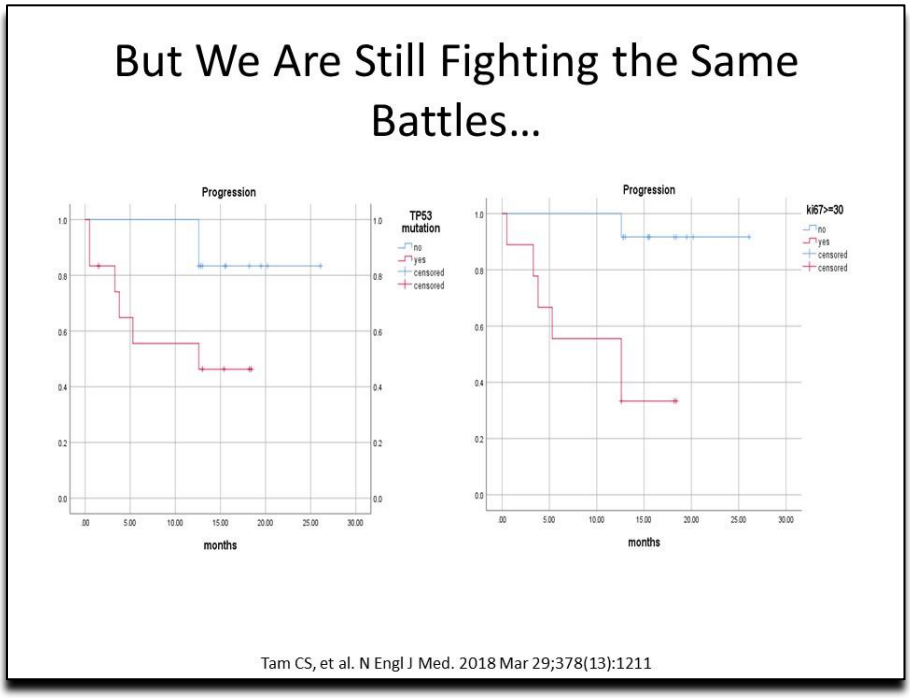
Ibrutinib + Rituximab

We've tried adding Rituxan®. It does work for some, but for those who have rapidly growing disease not so well.



Ibrutinib + Venetoclax

The same goes for venetoclax (Venclexta®) .

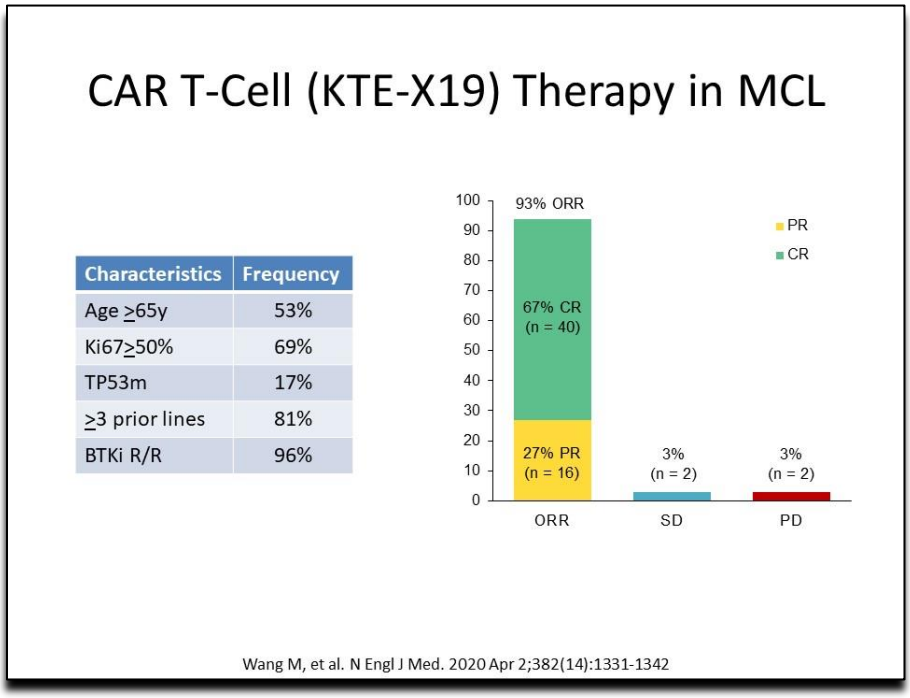


But We Are Still Fighting the Same Battles…

It works. But in those who have more rapidly growing or TP53 mutations, it works less well.

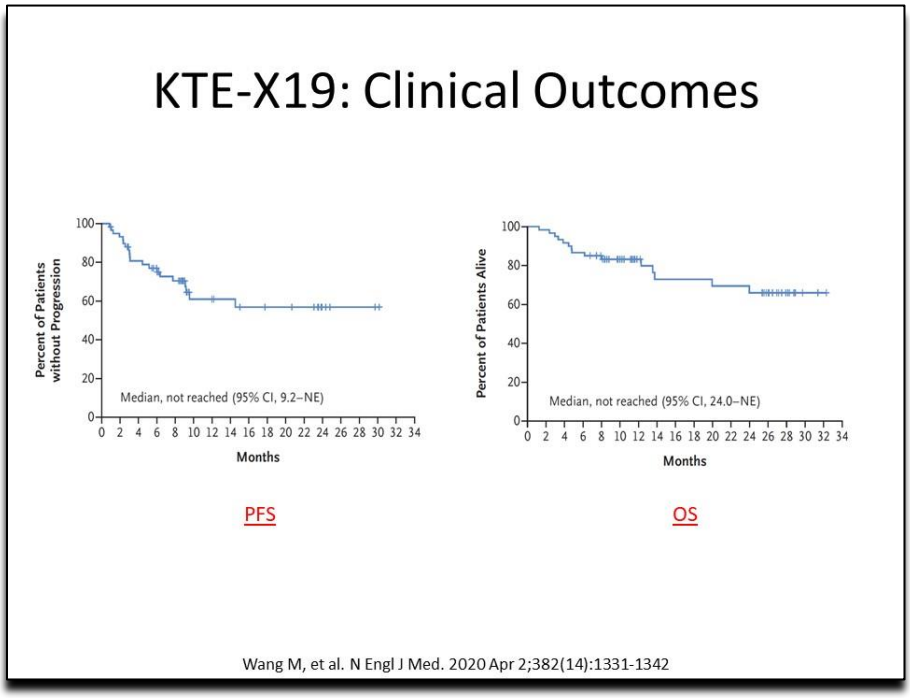
Can We Do Better?

So, can we do better? And the answer is, “I think so.” This is the exciting data that I wanted to share at the end.



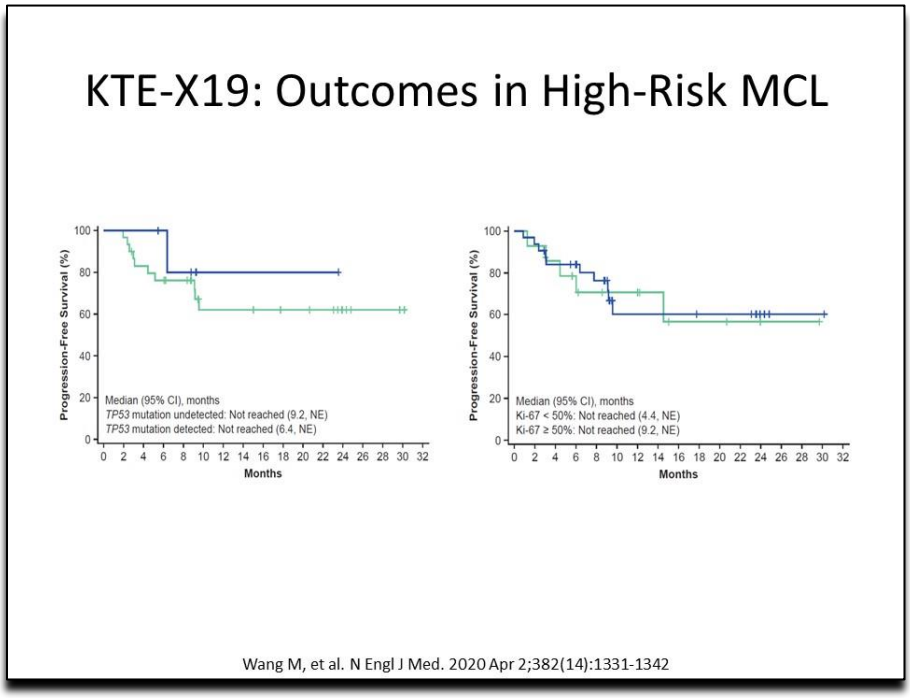
CAR T-Cell (KTE-X19) Therapy in MCL

You can see here that despite taking care of patients with very high growth rates—patients with mutations—we still got very high response rates.



KTE-X19: Clinical Outcomes

And more importantly, these response rates were durable meaning at 2 years about 60% are still in remission and are alive.



KTE-X19: Outcomes in High-Risk MCL

And you can see here that even for folks who had a TP53 mutation—that is the dark blue—or who had high growth rates, the benefit was the same.

How *"I Treat Relapsed & Refractory MCL"*

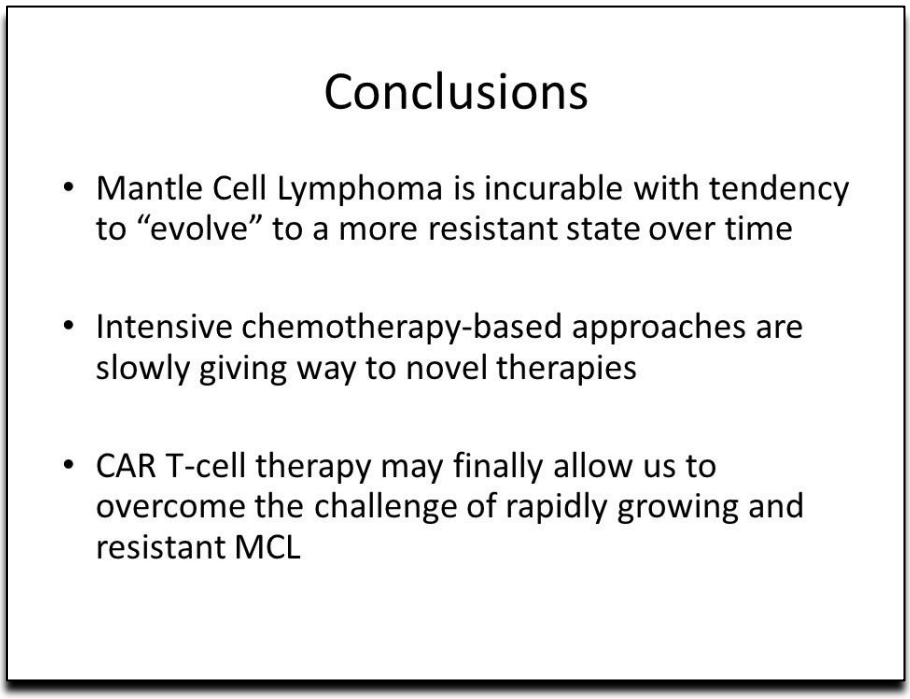
- Balance aggressiveness of disease with intensity of therapy, age/patient tolerance, and unique disease features
  - Aggressive
    - Induction: BTKi + Rituximab +/- Venetoclax, VCR-CVAD/VRCAP, RBAC, CAR T, Clinical Trial
    - Consolidation: Allogeneic Transplant
  - Non-Aggressive
    - Induction: BTKi +/- Rituximab, Lenalidomide+Rituximab, Bendamustine+Rituximab, Clinical Trial
    - Consolidation: Maintenance Rituximab

How "I Treat Relapsed & Refractory MCL"

Where Are We Going Next In MCL

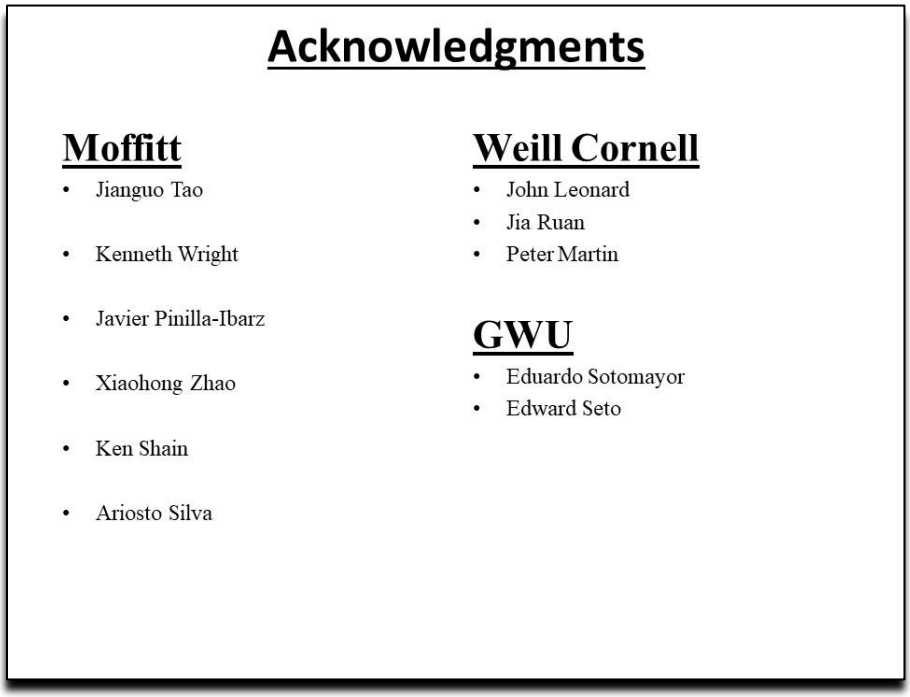
- General Themes
  - Improve Tolerance
    - Low Intensity Chemotx + Novel Agent(s)
    - Replace Chemotx with Novel Agent(s)
  - Optimize the duration and intensity of maintenance
    - Rituxan *vs* Rituxan + Novel Agent(s)
    - CAR T-cell Therapy

Where Are We Going Next In MCL



Conclusions

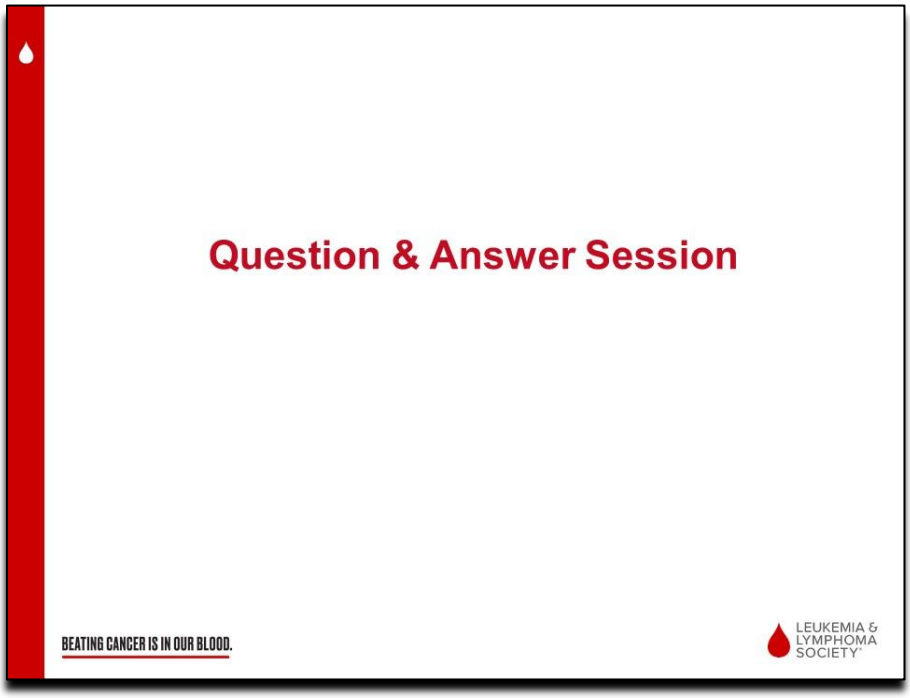
So, this is a very quick summary. And so, with that I just want to say quickly, mantle cell is incurable—tendency to evolve to a more resistant state over time. Intensive chemotherapy is giving way to novel therapies. And CAR T is something I'm very excited about.



Acknowledgments

Thank You!!

So with that, thank you. This concludes my presentation.



Question & Answer Session

Ms. Lizette Figueroa-Rivera
Thank you so much, Dr. Shah. And it's now time for our question-and-answer session.

Doctor, the first question comes from Terry. Terry asks, "I'm currently on watch-and-wait for my indolent mantle cell lymphoma. What are the symptoms that you look for to proceed with treatment?"

Bijal Shah, MD
The number-one thing I'm looking for is symptoms. Is someone having more in the way of fevers, soaking night sweats, losing weight without trying to? Those who have more indolent mantle cell lymphoma don't tend to have very much in the lymph nodes, but they do tend to have a big spleen. And that spleen can push on the stomach, can interfere with appetite. And also, as that spleen gets bigger, can come with low blood counts. Think of it acting like a sponge, soaking up those red blood cells and white blood cells and blood-clotting platelet cells. And so, if I start to see those symptoms emerge that's usually when I'm starting to say, "It's time to start thinking about therapy."

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

Operator
Our question comes from Gerald calling from Maryland. Please go ahead with your question.

Gerald
Hello, my name is Gerald. I am a 13-year survivor of mantle cell. I had high-dose Cytoxan as my treatment. But now, I have end-stage kidney disease, and I wanted to know if my disease is related to my original treatment.

Bijal Shah, MD
I think that's a great question and not an easy one to answer. When I think about high-dose Cytoxan, I think more about the bladder and less about the kidneys. But you bring up a very good point, and that is there's a cost that we pay when we treat very intensively.

And that's one of the reasons why I think many of us are starting to say, if we have less-intensive alternatives—again, we have to use them more chronically—but if we have less intensive alternatives like ibrutinib, like acalabrutinib, like zanubrutinib, like venetoclax or lenalidomide, we want to start thinking about how we bring them forward so we can avoid being in this situation.

Now it doesn't mean that we get out of every bad situation. There can be side effects with the newer drugs. But they don't tend to be as longer-lasting. So, think of it as any other pill. You take it, you stop taking it, and the pills wear off.

Ms. Lizette Figueroa-Rivera
Thank you, Gerald, for that question. And we'll take the next question from our telephone audience, please?

Operator
Thank you. Our next question comes from Gina, calling from Connecticut. Please state your question.

Gina
I was treated in 2009 for R-CHOP, two 3-day treatments with RICE and then a 6-day regimen of BEAMand an autologous stem cell transplant. And so that was 10.5 years ago—no follow-up rituximab. I go back every 6 months, feel really good, went into remission very quickly. One doctor said—at 7 years, he said—he used the word "cure." And then the next time I saw him he said, "Well, you should have only lived 3 years with this disease." So, it's kind of all over the place.

Bijal Shah, MD
Well, let me help a little bit. So, in the early 2000s, mantle cell got its name. Mantle cell wasn't really a defined entity. When we used an older classification system, the REAL classification, that was really discriminated. And we were learning. And as we were learning, we were trying things with different chemo regimens, and we didn't have a lot of options when folks relapsed. And so, yes, the survival was more poor-looking back then.

As we have gathered more experience, there's no question the survival has improved. I think that for now what I quote for most of my patients, particularly if they have low- or what we call intermediate-risk disease—I quote from a survival rate of about 10 years. That's our median. But you also bring up something that's really cool and that I also love to see. There's some people that we've treated who've gone on way longer than we would expect without relapsing.

And again, I have a few of those in my practice as well. And it's something I love to see but also not something that I can explain. It may be possible that with all that intensity that there is a small subset maybe it's 1%, maybe it's 5%—I'm not sure. But there may be a small subset that we actually can cure with mantle cell.

The hard part is we have this sort of pre-mantle cell–like phase—what I was kind of presenting in the beginning—that where the mantle cell can be very indolent or very dormant before it comes back. And so, we don't know whether that means you're cured or whether that means there can be a relapse that occurs 5 or even 10 years into the future. And so, I agree with ongoing follow-up.

Ms. Lizette Figueroa-Rivera
Thank you, Gina, for the question. Our next question comes from Leila. Leila asks, "After 3 years of maintenance Rituxan®, how long does it take for immunoglobulins to reach normal levels? Or does it never happen?"

Bijal Shah, MD
Again, a very good question and it's going to be different for every person. Mantle cell lymphoma is a part of the immune system. And so with that in mind, the immunoglobulins may not have been normal even before the mantle cell was treated. The other part is they have been what I call borderline—right?—just barely getting by. But now, as a consequence of the chemotherapy and the maintenance Rituxan®, now we've sort of taken away that limited reserve. And so the antibodies might not come back.

On the other hand, we've certainly seen cases where the antibodies do come back. And it can be variable. Anywhere from 6 months to a year is typically what I tell people. But, it's not an easy question to answer, and I think it's an area where we still have a lot to learn.

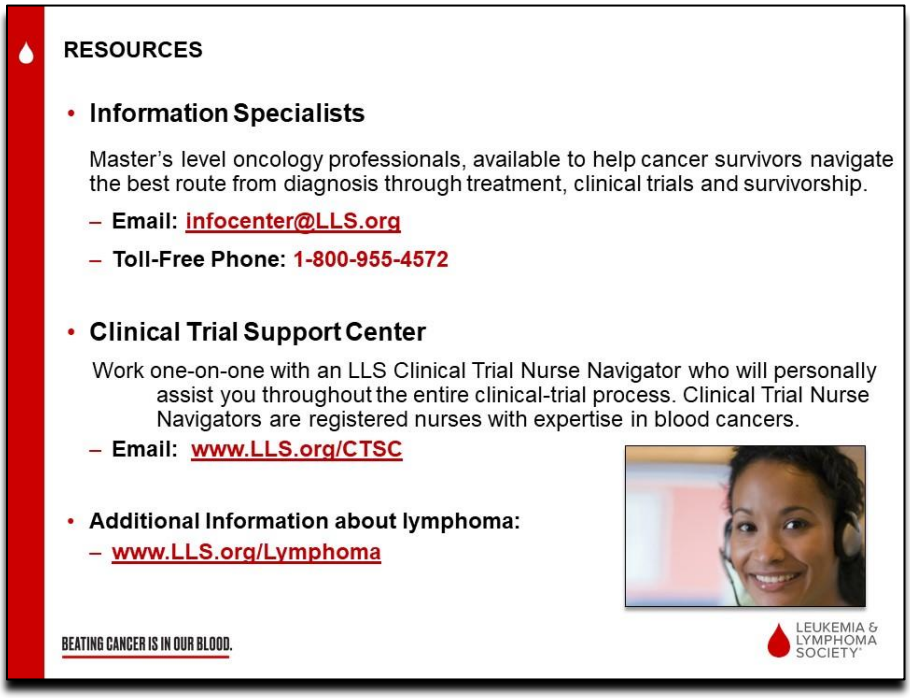
Ms. Lizette Figueroa-Rivera
Thank you. And Wanda is asking, "What are your views on oral treatment versus a chemo protocol for relapsed mantle cell in terms of durability of remission?"

Bijal Shah, MD
I think that it really depends more on the biology. And I apologize for taking so long to go through those slides. But that's really what I wanted to give people a flavor for, is that mantle cell is wildly heterogenous. And there's no two patients who present the same.

In general, I do tend to lean a little bit more on the oral medications when it comes back. But if it's—again—very rapidly growing, if there are other high-risk features that tell me the pills just aren't going to work or it's going to take too long for the pills to demonstrate the effect that we need and the disease may do something bad in that period of time, then I'm more likely to say this is a scenario where we need to at least think about some chemo. Maybe it's just one or two cycles, but some chemo then as a bridge to something else.

Ms. Lizette Figueroa-Rivera
Thank you. And I know in these times, it's difficult. And Jeffrey is asking, "What is your recommendation? Can a mantle cell patient not currently receiving chemotherapy visit with grandchildren living in the same city at this time?"

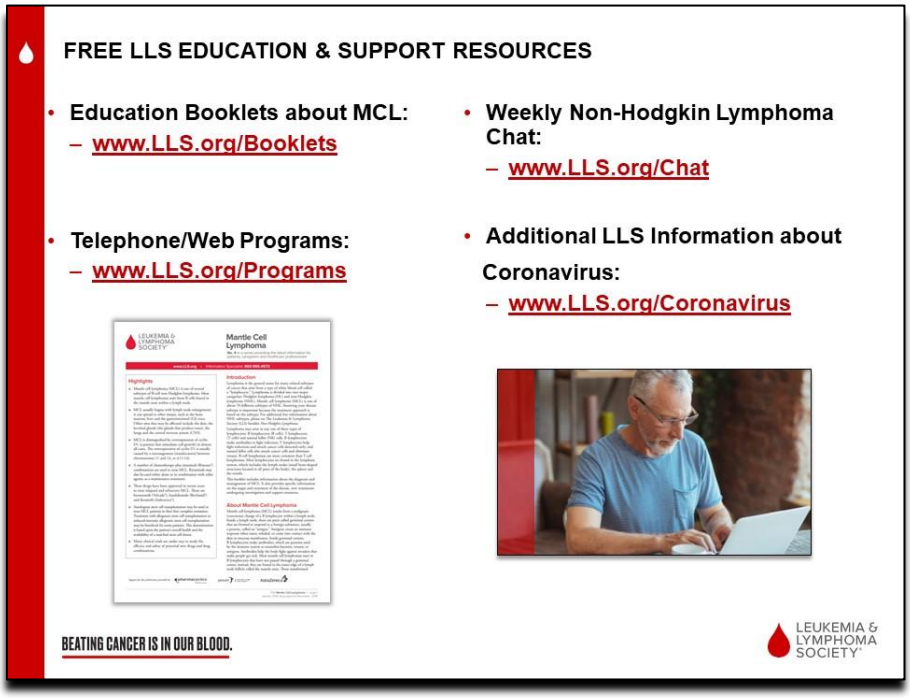
Bijal Shah, MD
Absolutely. Do you know what I tell people? Even with COVID, I think the key here is washing your hands, trying to avoid touching your face—simple precautions. I would love to tell everyone that we have an easy, fast solution for preventing COVID. And the answer is we don't. It's like the flu. And even though it's more deadly than the flu, it's like the flu in terms of how it spreads. And to that end, we just recommend the best we can is to try and practice those kinds of behaviors. If someone is sick, then that's the time to stay away. Otherwise, no. Go enjoy your grandkids.



Resources

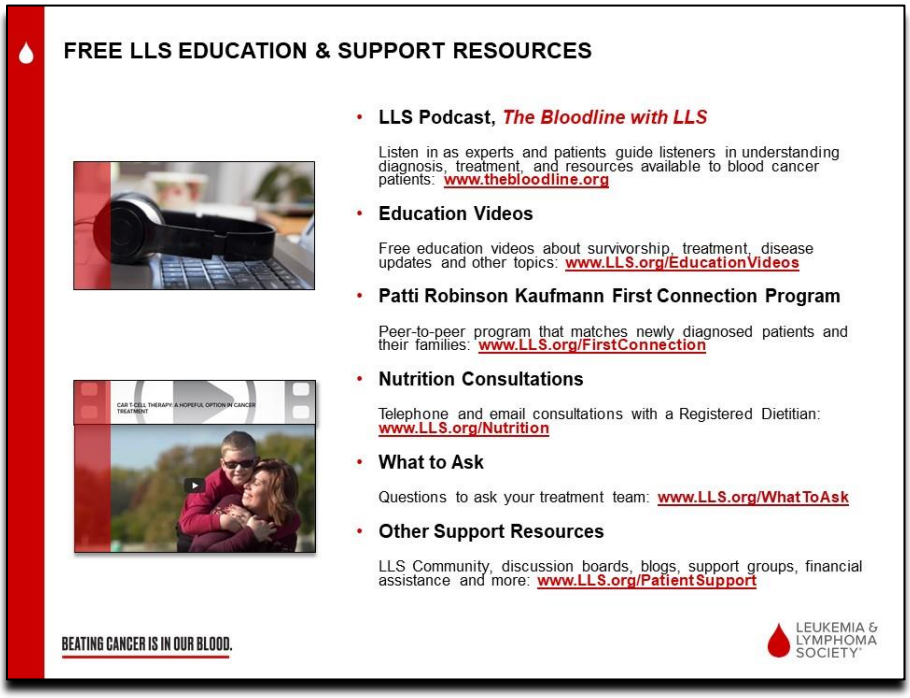
Ms. Lizette Figueroa-Rivera
Well, thank you so much, Jeffrey, for your question. And thank you all for your questions. A special thank you to you, Dr. Shah, for sharing your expertise with us and for your continued dedication to our blood cancer patients and their loved ones.

And if we weren't able to get to your questions today, please contact an Information Specialist at The Leukemia & Lymphoma Society at 1-800-955-4572. And we're available from 9:00 a.m. to 9:00 p.m. Eastern Time. Or you can reach us by e-mail at infocenter@lls.org. Information Specialists are available to answer your questions about treatment, including clinical trials, or answer other questions you may have about support, including financial assistance. We also have a Clinical Trial Support Center where Nurse Navigators can assist you with finding a clinical trial that may be appropriate for you. And you may also reach them at the same number, which is 800-955-4572.



Free LLS Education & Support Resources

Again, we'd like to acknowledge and thank Kite Pharma, Inc.; Pharmacyclics, an AbbVie Company; & Janssen Biotech.



Free LLS Education & Support Resources

Thank You

Dr. Shah, thank you again for volunteering your time with us today. And on behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. Please let us know what you need from us during this time and take good care.