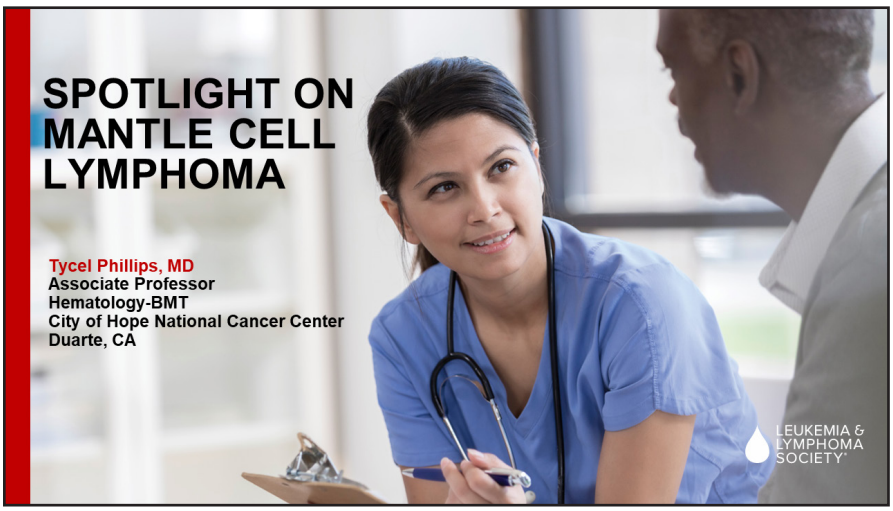
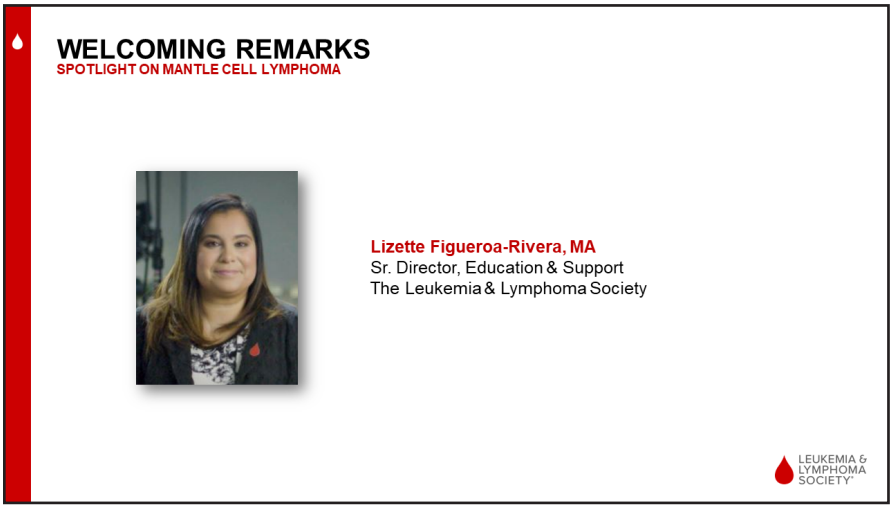


Slide 1: SPOTLIGHT ON MANTLE CELL LYMPHOMA



Slide 2: Welcoming Remarks

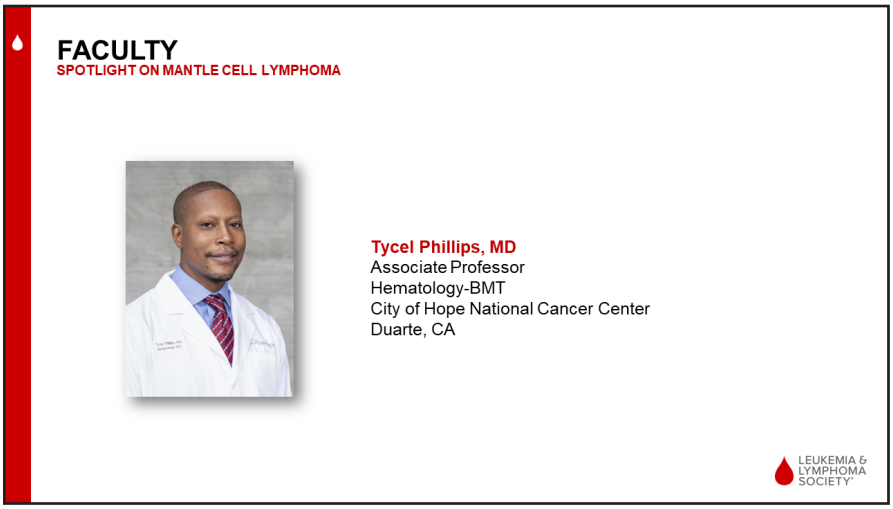
Lizette Figueroa-Rivera:

Hello, everyone. On behalf of The Leukemia and Lymphoma Society, I'd like to welcome all of you. LLS has invested over $1.5 billion in cancer research since our founding in 1949, leading to nearly every advancement in blood cancer treatment and breakthroughs in immunotherapy, genomics, and personalized medicine. LLS's current research portfolio contains 7 grants heavily focused on mantle cell lymphoma. Novel drug combinations and alternative cytotoxic-free regimens are being explored in mantle cell lymphoma. The goals are to find new avenues of therapies and to overcome resistance to existing therapies.

LLS helps patients navigate their cancer treatment and ensures they have access to quality, affordable, and coordinated care. Research will help us achieve an end to cancer. In the meantime, patients need help before, during, and after their diagnosis and treatment. Please continue to inform us of what you need during this time, and please continue to let us be there for you.

For this program, we would like to acknowledge and thank Eli Lilly and Company and Kite, a Gilead company, for their support of this program.

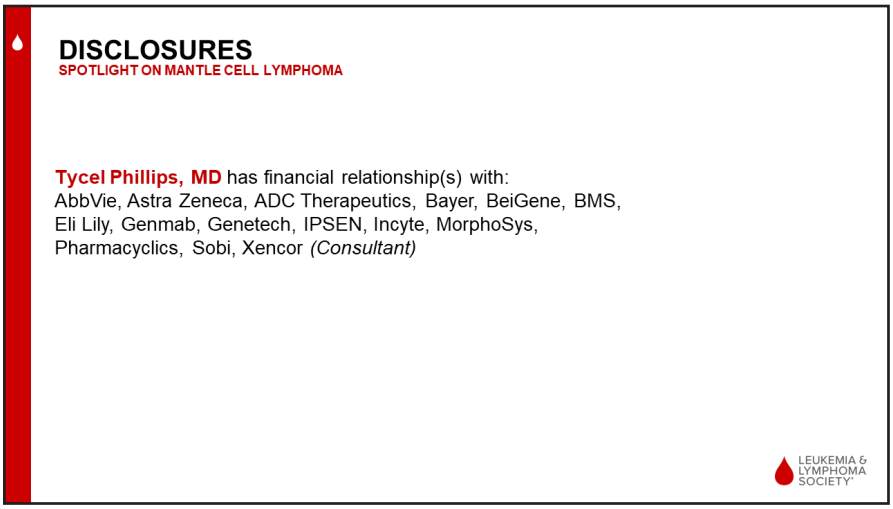
It is my pleasure to introduce Dr. Tycel Phillips, Associate Professor at City of Hope National Cancer Center in Duarte, California. Dr. Phillips, I'm privileged to turn the program over to you.



Slide 3: Faculty

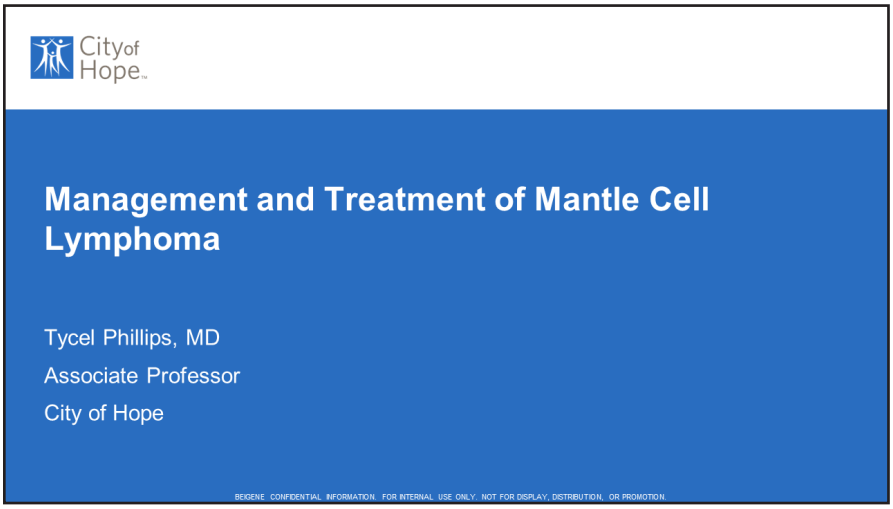
Dr. Tycel Phillips:

Thank you everyone for joining and thank you for the invitation to speak today. I'm looking forward to a robust discussion.



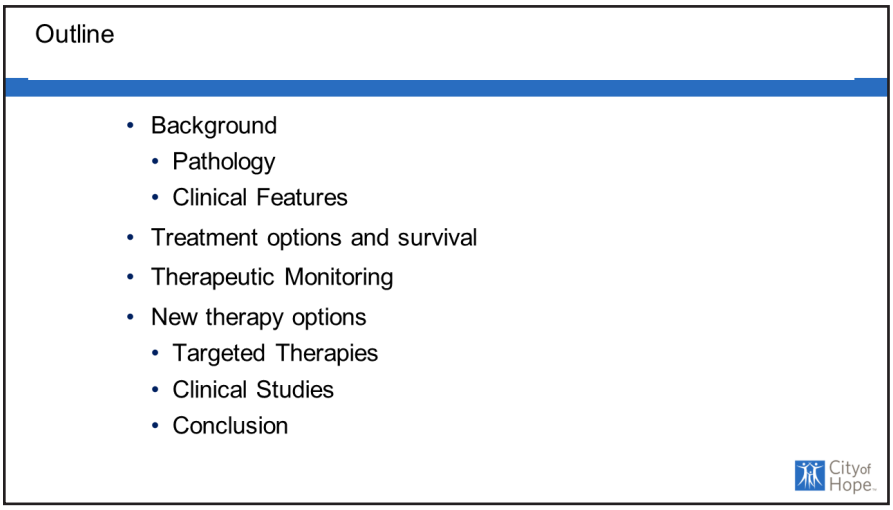
Slide 4: Disclosures

Here are my disclosures.



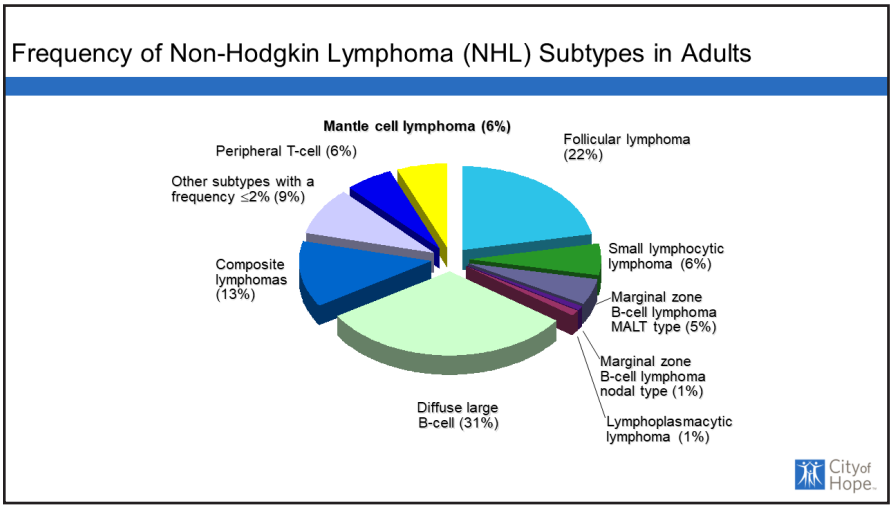
Slide 5: Management and Treatment of Mantle Cell Lymphoma

Today we will talk about the management and treatment of mantle cell lymphoma. The next slide will give an overview of some of the things we'll talk about.



Slide 6: Outline

We'll go over some background information, treatment, and then we'll look at options with targeted therapies. Some of the trials that are being conducted and we'll conclude and open up for questions and answers.

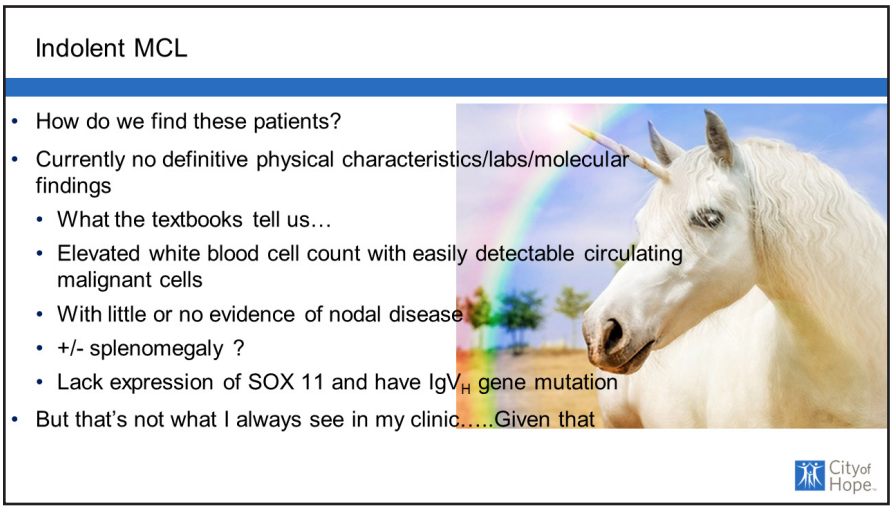


Slide 7: Frequency of Non-Hodgkin's Lymphoma (NHL) Subtypes in Adults

A lot of you have probably seen this pie chart before, looking at non-Hodgkin's lymphoma subtypes. As you can see, the most prevalent form of non-Hodgkin's lymphoma is diffuse-cell lymphoma, followed by follicular lymphoma. Mantle cell lymphoma is rare, accounting for 5% to 8% depending on which reference you're looking at, as far as the non-Hodgkin's lymphoma subtypes. It is generally thought to have a higher male-to-female prevalence, either 3 or 4 to 1, generally in patients 65 and older, and patients of European ancestry by literature tend to have a higher incidence of the disease as compared to other ethnic groups.

The pathognomonic marker of mantle cell lymphoma is either the presence of cyclin D1 or the presence of the 11;14 translocation on FISH analysis. In certain patients, cyclin D1 is not present or they cannot find the 11;14 because it is really subject to where the breakpoints are on the chromosomes. The marker SOX11 hasn't really been utilized lately in cases where we have cyclin D1 negative mantle cell lymphoma. The true essence of cyclin D1 negative is probably not correct, as a majority of these other patients are probably having their mantle cell lymphoma driven by a different cell cyclin, as there are reports of cyclin D2, D3 being noted to be in cases that are thought to be cyclin D1 negative.

In essence, all of this leads to the proliferation of the malignant clone, but each of these events is not enough to cause a cancer, so there are other mutations that happen which lead to the development of mantle cell lymphoma, even though we always look for 11;14 and cyclin D1, that is really not enough to cause a normal cell to transform to a cancerous cell. With mantle cell lymphoma, I think one of the biggest things that we've encountered lately is that historically we used to always consider all patients as needing to be treated and we assumed that everybody had very similar outcomes.

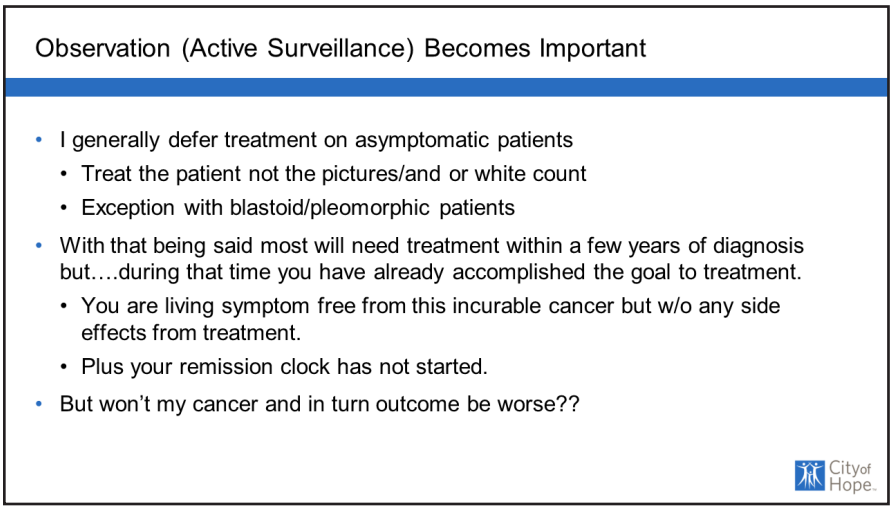


Slide 8: Indolent MCL

I think over the last couple of years, we've been well aware that there are different outcomes based on patients' presentation, genetic features, mutational analysis, to the point where we now know that there are probably 3 distinct subgroups of categories of patients with mantle cell lymphoma, and likely more as we get more information. The first one I always like to talk about is the indolent patient with mantle cell lymphoma. This accounts for about 10% of the patient population. I include this unicorn diagram in the sense of, even though we know indolent mantle cell lymphoma patients exist, we can't really completely identify these patients when they are present in the clinic.

This is something that really plays out in time as the patient's disease course and clinical presentation will dictate whether these patients are indolent or not. As is the case with a lot of these lymphomas that are not curative, like mantle cell lymphoma, we do know that patients have likely been living with these cancers for quite a bit of time before we diagnosed them. Almost all patients will have a period where we would consider them indolent because they are living without symptoms related to the cancer, but if you look in the textbooks, they typically identify based on information from the Spanish group that patients with indolent lymphoma are the non-nodal leukemic variants of mantle cell lymphoma, meaning these patients have enlarged spleen, circulating cancer, and bone marrow involvement.

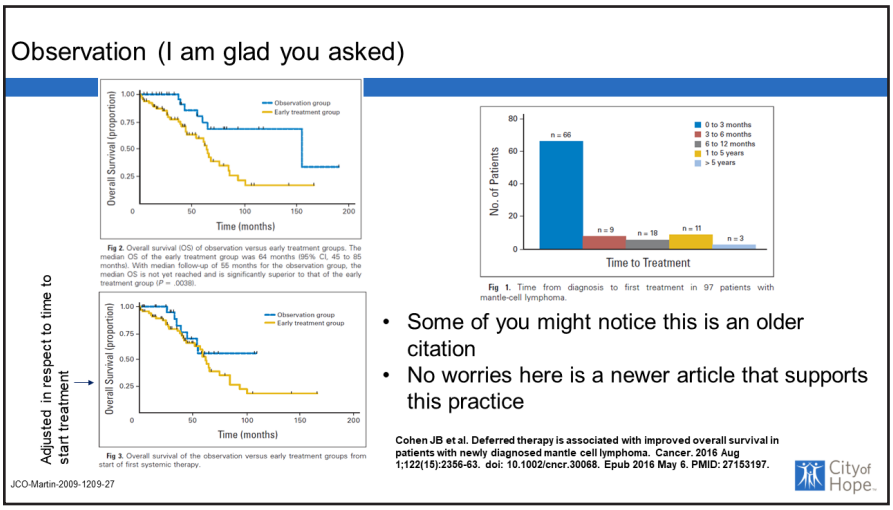
These are the ones that are more closer to or sometimes confused with patients with CLL (chronic lymphocytic leukemia). These are the ones that we typically think are the indolent patients. These patients also are thought not to lack the expression of SOX11 and may have IGH (immunoglobulin), heavy chain rearrangements, or mutation. In my clinical practice, I've seen patients with non-nodal leukemic variant and also patients with nodal disease who have had quite a bit of time of observation and management and monitoring. I do think at this point in time, we don't really know how to identify an indolent patient, but a situation that plays itself out. To that end, it brings up the next point of what happens when a patient presents to the clinic.



Slide 9: Observation (Active Surveillance) Becomes Important

Typically when we think about mantle cell lymphoma, I'm sure most patients don't typically think about observation or active surveillance, as some people like to refer to it but in general, in my practice, and based on what I've known, if a patient is asymptomatic, generally I will try to defer treatment in these patients other than the patients who may have blastoid or vertical pleomorphic variant mantal cell lymphoma, which is considered to be quite aggressive. The question of why to observe, well again, we know mantle cell lymphoma outside of some rare cases or in the use of allogeneic stem cell transplantation, is not a curative cancer.

It is something we treat, we manage, we put patients into remission, but for the most part, we do know the cancer will come back, but generally when we treat, we are treating to fix a problem. Whether a patient has fevers, night sweats, painful splenomegaly, or early satiety, there is some issue we're fixing to try to improve for the patient to enjoy their quality of life while they're in remission. Those who are without an issue, then obviously there is really nothing for us to fix. So we are giving you side effects to just get you back to where you started. That has not been a practice of mine over the last several years, if not longer, to treat patients without symptoms, unless again, they have very aggressive disease at the start. The other benefit of this is that, if we don't treat you obviously you are living a remission period without starting treatment, but your remission clock has not started. Obviously, the concern will always come back to the simple fact we've always been trained in our minds to say, if you have a cancer it should be treated, removed, or whatever. They also thought that by not doing anything with my cancer, then my cancer is going to get worse.

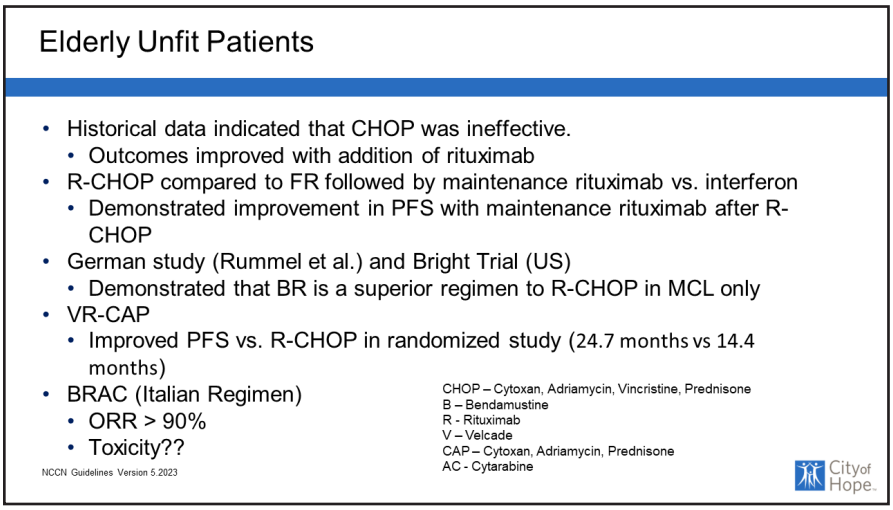


Slide 10: Observation (I am glad you asked)

Thankfully, there is data that supports that observation has no detrimental effect to the long-term outcomes of a patient with mantle cell lymphoma. As we see, this early study from the Cornell Group compared patients without aggressive features, so no blast or no pleomorphic, these patients were either treated at diagnosis or observed. As you can see from the 2 Kaplan-Meier plots, the blue and the gold curves, you see that it appears that the observation group actually had a better survival than the patients in the early treatment group.

Now that the top graph is really subjective to lead time bias, remember we talked about the remission clock? When we start treatment, that clock starts to tick. If you adjust both those patient populations from survival based on time of treatment, the survival curves look very similar or superimposable. Again, indicating there is no detrimental effect to observing patients if they don't have symptoms. If you look to the right, as you see, the majority of the patients were treated within 0 to 3 months. That is typically what we expect with most patients with what we call classic mantle cell lymphoma, that we expect most of these patients we observe will at some point within a year require treatment.

As you look to the right, you'll see that there are a smattering of patients who are observed from 1 to 5 years and then greater than 5 years. Some of these patients that are asymptomatic, irrespective of presenting symptoms, will have a very long course where we can monitor these patients without actually having to start treatment. Now, as some of you may astutely notice, this article from Dr. Martin is from 2009. Just to be reassured, there is a more recent publication that also supports that deferred therapy is associated with improved overall survival. That is not likely related to the fact of observation is better, but the simple fact that patients who can't be observed should be observed because their cancer is probably not super aggressive and does not warrant any urgent treatment or treatment right at diagnosis.



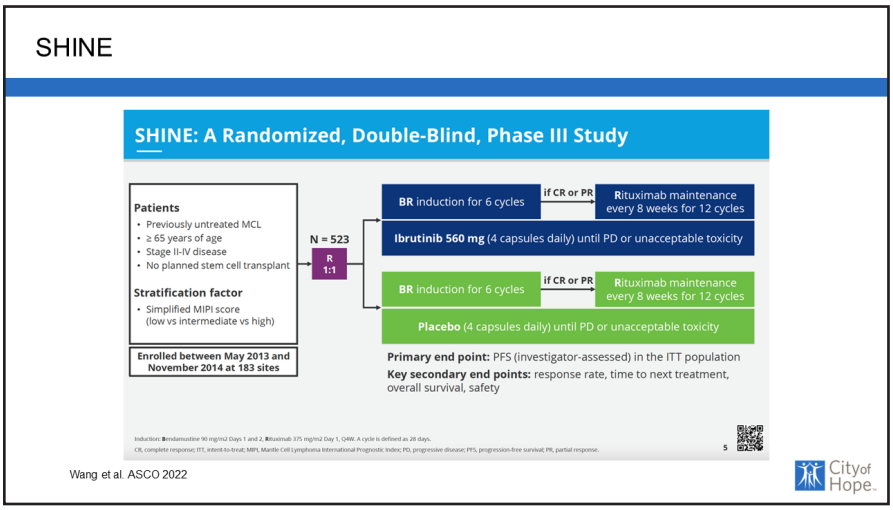
Slide 11: Elderly Unfit Patients

Observation is something that you should more than likely talk about with your clinical practitioner, whoever is taking care of you, especially if you are asymptomatic. There is no rush to start therapy. Now, for those who need therapy, for the most part, there is not a standard of care. When you look at patients with mantle cell lymphoma, we generally will segregate treatment into a young fit or older and unfit category. For those patients who are older and unfit, historically, a lot of the treatment has been based on CHOP-based regimens. Obviously, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is a standard of care treatment for diffuse large B-cell lymphoma. We've used it for follicular lymphoma, and so it was obviously something that was utilized in mantle cell lymphoma.

Some of the early studies that came out of a German group compared R-CHOP to fludarabine (Fludara®) and rituximab (Rituxan®). This study showed that R-CHOP plus maintenance rituximab was a better treatment regimen than fludarabine and rituximab, irrespective of what was given for maintenance. More recently, there was a German trial that came from Dr. Rummel that was replicated in the United States called the BRIGHT trial, which compared R-CHOP to bendamustine (Bendeka®) and rituximab, or R-CHOP to RCVP (rituximab, cyclophosphamide, vincristine, prednisone) to bendamustine and rituximab. Both of these trials indicated patients with mantle cell lymphoma had better chemotherapy drug for mantle cell lymphoma than R-CHOP.

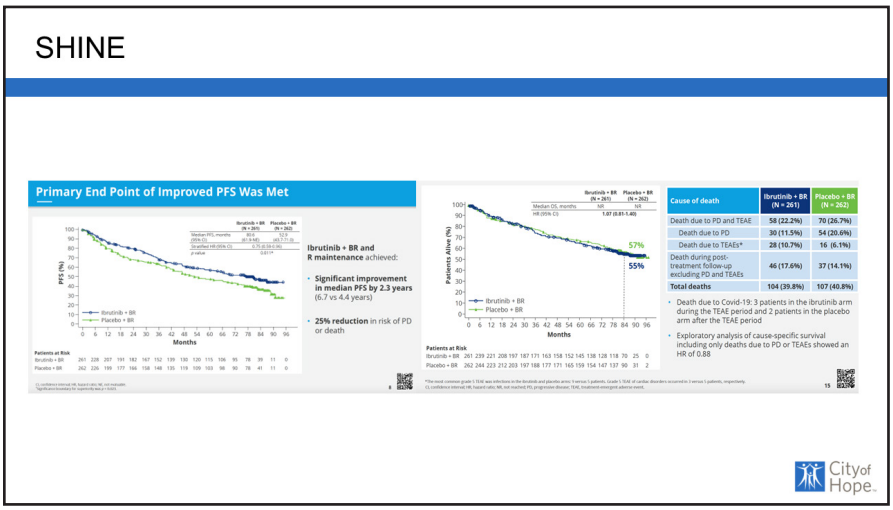
From that point forward, bendamustine and rituximab has really been the backbone of treatment for patients who were not considered to be candidates for more aggressive therapy. Subsequently, we've had other clinical trials that looked at modifications of R-CHOP. We have VR-CAP, which adds Velcade® (bortezomib) to R-CHOP which just replaces the vincristine. This randomized trial did show that VR-CAP was a better regimen than R-CHOP, with an improvement in progression-free survival, a suggestion of an overall survival benefit.

The Italians had looked to soup up bendamustine and rituximab and added Ara C to that regimen, so-called BRAC. This regimen had a very high overall response rate but did have significant toxicity due to the fact that cytarabine can sometimes be a very hard drug to tolerate as we get older. They made several modifications to this regimen to try to improve the tolerability. What we do know, it is effective but it does have more toxicity than bendamustine and rituximab alone. To date, it has not been compared to BR alone in mantle cell lymphoma patients.



Slide 12: SHINE

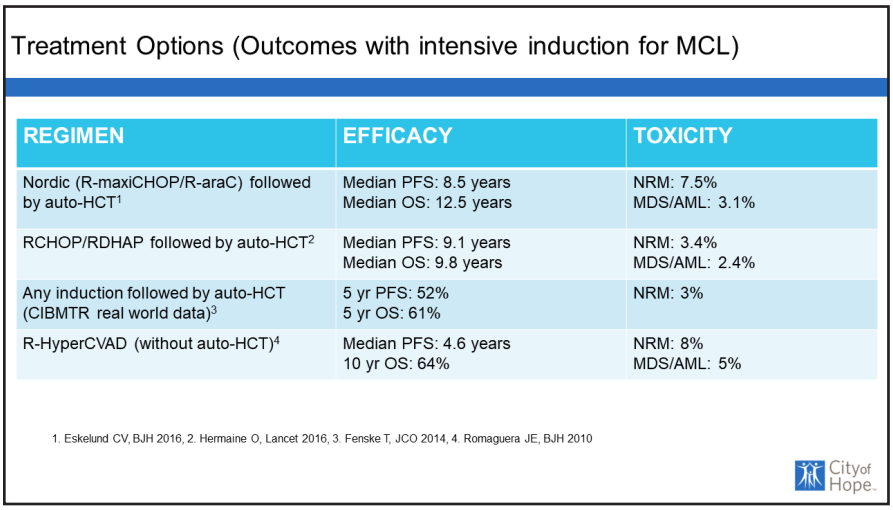
Now, some of you will remember there was a large trial of the SHINE study, which was bendamustine and rituximab plus a BTK (Bruton's tyrosine kinase) inhibitor. This study read out in ASCO (American Society of Clinical Oncology) 2022, 523 patients with newly diagnosed mantle cell lymphoma not eligible for an autologous stem cell transplantation. Patients were randomized to either BR alone followed by maintenance rituximab, or BR plus ibrutinib (Imbruvica®), which was continued until intolerance or disease progression.



Slide 13: SHINE

The key points from this trial is that there was a progression-free survival benefit with the use of ibrutinib in this patient population, with a PFS of 6.7 years versus 4.4 years. I'm sure some of you will ask us, "Why has it not become the standard of care?" If you look to the curve to the right, you see there's not a survival benefit with the implication and utilization of ibrutinib in combination with bendamustine and rituximab. This is due to non-cancer-related deaths.

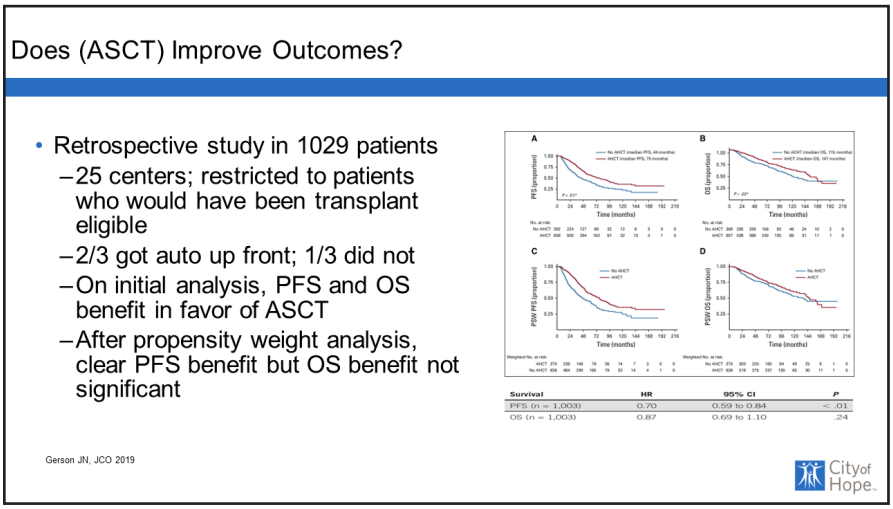
There was significantly more non-cancer-related deaths in the experimental arm, which is BR and ibrutinib, which impacted the overall survival based on that information and a lack of real insight into what was causing these deaths. A lot of people speculate that if you give BR and sequentially give a BTK inhibitor, you will likely get a very similar PFS. This was actually demonstrated in a retrospective real-world study. Because of that, this study has not necessarily been something that most physicians have recommended. Actually, because of this trial, ibrutinib is no longer FDA-approved or even utilized in patients with mantle cell lymphoma as it lost its indication.



Slide 14: Treatment Options (Outcomes with intensive induction for MCL)

If we look to patients who are considered to be younger or fitter or basically eligible for an autologous stem cell transplantation, which typically means patients 75 or younger without any significant comorbidities, you see there are a smattering of very intensive regimens from the Nordic regimen to alternate R-CHOP/R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) or DHAOx (dexamethasone, cytarabine, oxaliplatin). Again, hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone), which all have demonstrated very similar rates of efficacy.

As you can also see, these treatment regimens are also saddled with the same similar amounts of non-treatment-related mortality and toxicity, including secondary MDS (myelodysplastic syndromes) and AML (acute myeloid leukemia). For this point, there's been a lot of controversy and discussion about the best induction regimen for younger patients, and also, whether the utilization of autologous stem cell transplantation is actually needed in all patients with mantle cell lymphoma.



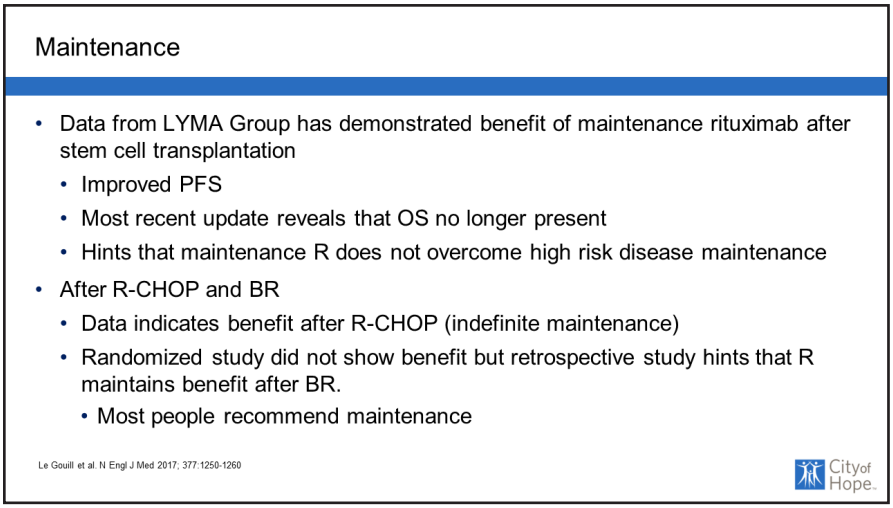
Slide 15: Does (ASCT) Improve Outcomes?

The one question we can always ask, autotransplant after consolidation of a high-dose chemotherapy has never been shown to have a survival benefit. It has been shown to have a progression-free survival benefit, but overall survival, patients who get a transplant are not living longer than patients who do not get a transplant. We've had

several studies. There's also a study from 2019 that looked at outcomes between patients who did and did not get an autotransplant.

Initially it looked like there was a PFS and overall survival benefit in favor of autotransplant, but after further analysis and correction of some discrepancies between the 2 treatment groups, the overall survival benefit went away, which is very consistent with what we have seen historically. There was not a survival benefit to autotransplant.

Given that and given some of the complications that can come with an autotransplant, the push and the lean of the clinical practice to date has been to move away from an autotransplant. We've had several clinical trials that have looked at alternative ways to consolidate and manage patients with mantle cell lymphoma with or without transplant. Some have shown that transplant is not necessarily beneficial in a lot of patient populations.



Slide 16: Maintenance

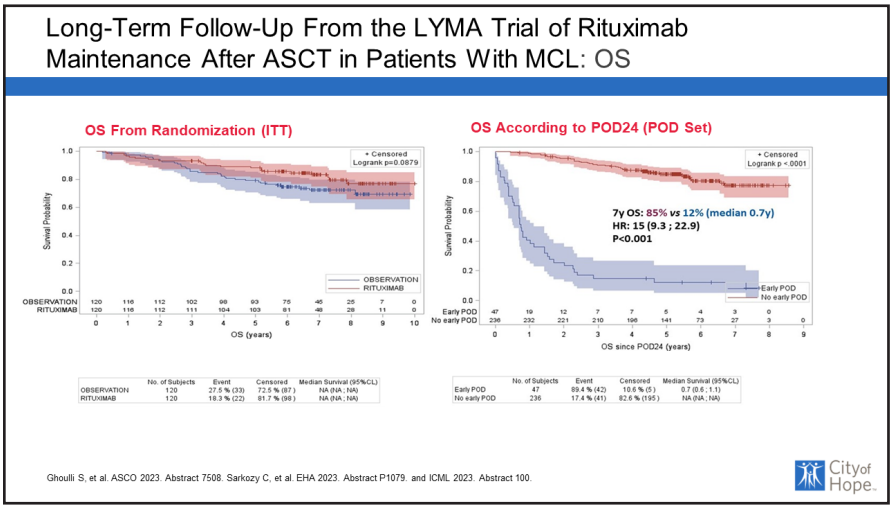
The one thing we do know is maintenance has shown to be very beneficial. After any intensive induction therapy and autotransplant, the LYMA Group showed that there was a progression-free survival benefit, and initially, there was an overall survival benefit to utilization of maintenance rituximab, and that's rituximab given every other month for 2 to 3 years. Most patients typically get 3 years.

At a recent update, the progression-free survival benefit maintains in this patient population, but the overall survival benefit is no longer present. What they did find out is that patients who are on the rituximab maintenance arm, who did have relapses, those patients tend to have worse outcomes. The speculation is that the patients who are relapsing on rituximab maintenance have more aggressive disease obviously, given that they are breaking through this treatment, which was leading to the worse outcomes.

We did discuss earlier that rituximab maintenance after R-CHOP has shown to be beneficial. The Germans have shown that indefinite rituximab maintenance after R-CHOP will continually call to a benefit in a progression-free survival. For those of you who have already received rituximab, there is no such thing as a free lunch. There are complications and side effects that come from rituximab, a lot of which we did realize in the COVID pandemic. Indefinite R-CHOP is not necessarily something that is utilized in most patients given the risk that comes from viral infections and other complications from rituximab.

After bendamustine and rituximab, there was a randomized trial conducted in Germany that initially suggested that there is no benefit to rituximab maintenance after bendamustine. There was a lot of criticism of this trial. To date, we don't have another prospective study that has shown a benefit, but retrospectively people who have looked at rituximab maintenance after bendamustine, and a lot of them have shown that it does appear that there

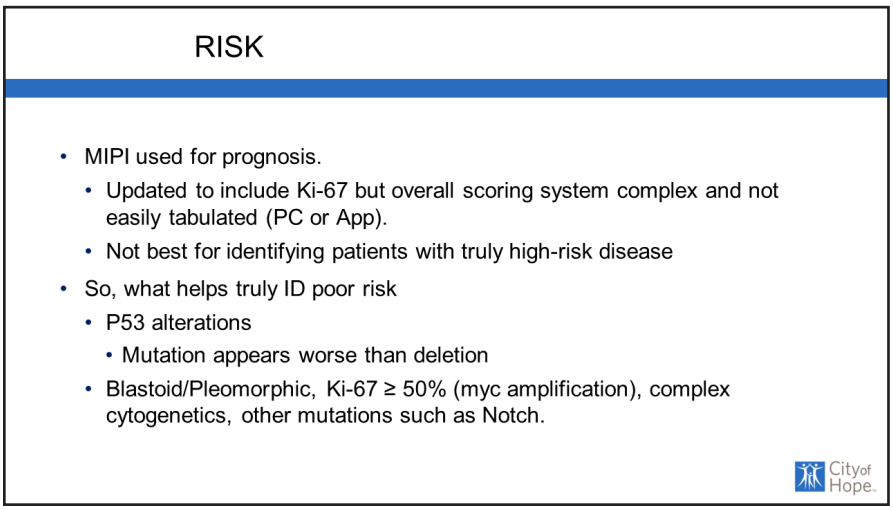
is still a benefit to rituximab maintenance. For that part, most people will recommend rituximab maintenance after bendamustine irrespective of what that clinical trial showed.



Slide 17: Long-Term Follow-Up from the LYMA Trial of Rituximab Maintenance After ASCT in Patients With MCL: OS

As I mentioned to you before about the loss of overall survival benefit after autotransplant, if you look here to this situation, patients who have an early relapse tend to have worse outcomes. This played out in the rituximab group where patients who relapsed early on the rituximab maintenance had worse outcomes than those who did not actually receive rituximab maintenance. Likely for the simple fact that, in this patient population if you're breaking through rituximab maintenance, you are likely to have more aggressive disease.

Part of the push and the lean away from autotransplant besides the complications, comes from risk groups that we know will not actually benefit from an autologous stem cell transplantation, and some of these patients actually probably do not benefit from chemotherapy at all. When we talk about risk, I'm sure everybody's familiar with the MIPI (Mantle Cell Lymphoma International Prognostic Index) score, and now we have the MIPI-C, which actually adds the Ki-67 (a marker of disease spread). Unlike FLIPI (Follicular Lymphoma International Prognostic Index) and the IPI (International Prognostic Index) score, this is not something we can easily calculate within a clinic.



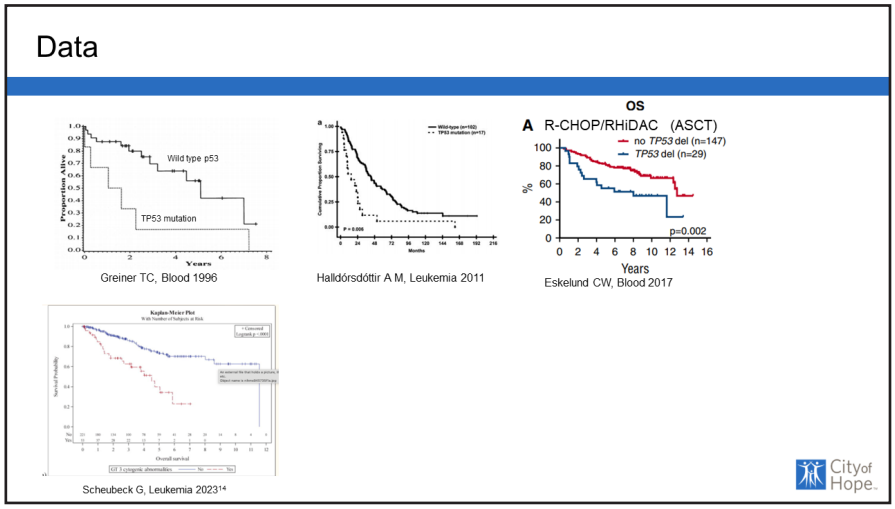
Slide 18: RISK

If you've seen any of your physicians calculate a MIPI score, they're likely either looking on a computer or open up a phone or app to calculate this, taking into account your white count, your LDH (lactate dehydrogenase) level, your Ki-67, your

stage of disease, and your age. The question is that a lot of us will calculate a MIPI score, but a lot of us are not basing our treatment off of a MIPI score. Then there is some more recent data suggesting that maybe high-risk patients with a high MIPI score may not necessarily benefit as well from chemotherapy as patients with intermediate and low risk but for the most part, a lot of us think that the MIPI scores don't really identify with truly high-risk patient. These high-risk patients are generally those with p53 alterations.

A lot of you are aware of 17p deletions, which leads to allele loss which leads to a loss of p53, but also we've found in the last several years that p53 mutations actually appear worse than the 17p deletions because this mutation is what we call a dominant negative, meaning the presence of this abnormal clone inactivates the good clone and also causes both to malfunction, meaning you have no function in p53. With the 17p deletion you have issues of monoallelic versus biallelic, meaning you lose one allele or two. If you lose one allele, you still have some functioning capacity, whereas if you lose both, you have none.

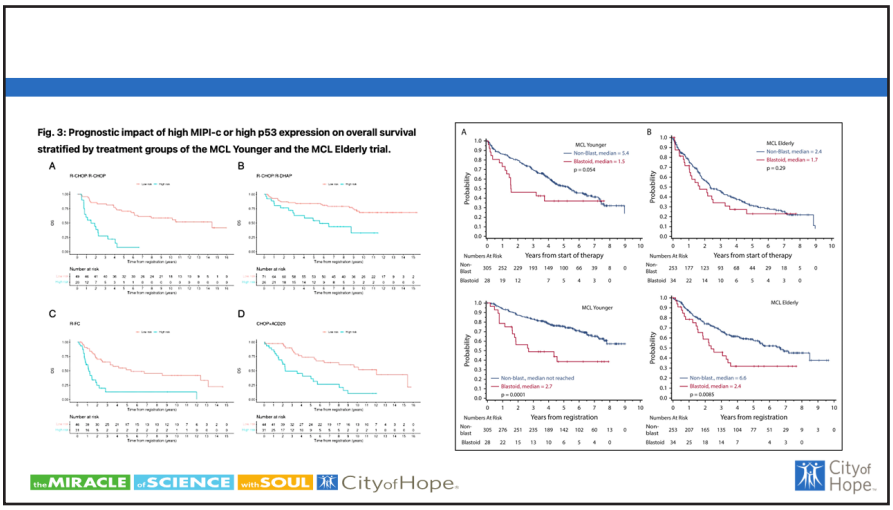
There's also, as we mentioned before, a blastoid/pleomorphic variant which morphologically appear more larger or aggressive cells than what we typically see, which are small round cells with mantle cell lymphoma. We have the proliferation rate of Ki-67, which most people speculate if you have something that's equal or greater than 50%, it causes more aggressive disease. Historically, we had always thought 30% was a cutoff, but the data tends to suggest that 50% is the appropriate cutoff now. Some data has linked that MYC (gene) amplification has been associated with poor outcomes, but MYC amplification is probably a surrogate marker for an elevated Ki-67, if you look on multivariate analysis, these 2 wash each other out.



Slide 19: Data

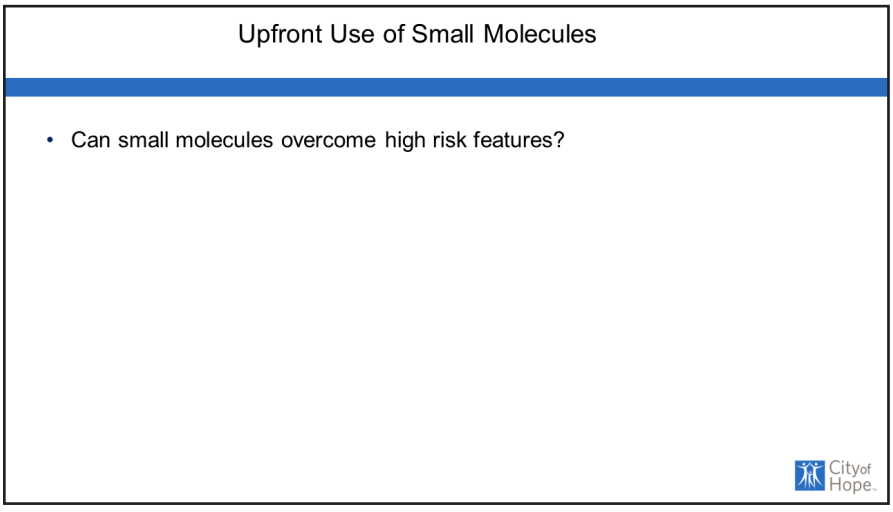
Complex cytogenetics is also a risk factor and there are other mutations, such as NOTCH and SMARCA4 that have shown to be poor risk factors. A lot of things we're finding out are impacting clinical outcomes. The important thing with these clinical outcomes, if you look at some of these graphs, p53 mutated patients do worse irrespective of what induction therapy we do. As you see, 3 trials at the top looking at p53 mutation with variant regimens of chemotherapy, and all these trials of patients who have a p53 mutation do worse than those with a p53 wild type.

The curve on the bottom, you may not be able to see so well, but the blue curve is patients without complex cytogenetics. The red curve is those with complex cytogenetics. These patients with complex cytogenetics have worse outcomes than those who don't with chemotherapy treatment. The curve to the right looks at patients either with a high MIPI-C score or a high p53 expression. High p53 expression is a surrogate marker, a little bit faster to get results to evaluate for a p53 mutation. It's about an 80% concordance between IHC (immunohistochemistry) and the gold standard, which is molecular testing.



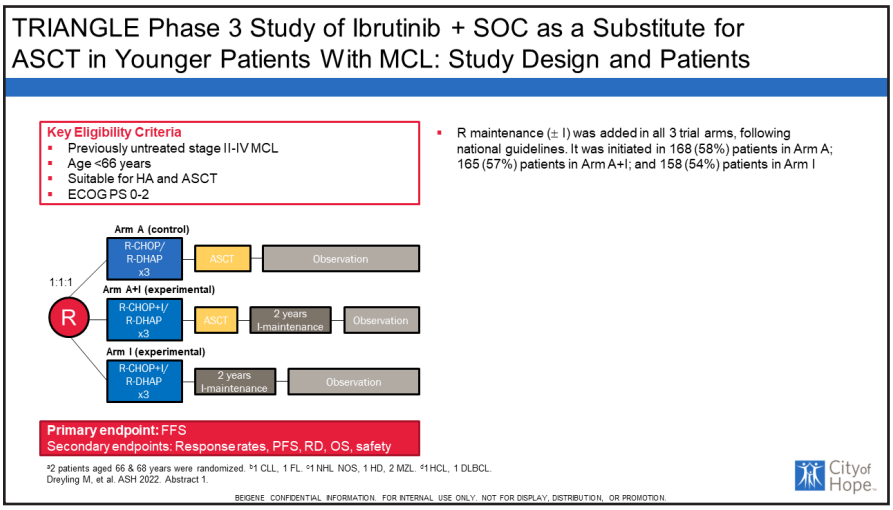
Slide 20: Data

In this one, they use IHC for a p53 evaluation. Again, they noticed that patients who have high p53 expression or high MIPI-C score do worse than others who do not, irrespective of the chemotherapy background. The curve to the right looks at patients with blastoid or non-blastoid. The curve with red is the blastoid variants. These patients tend to do worse than those who do not have blastoid variant. With the 2 studies, MCL younger, MCL elderly, the younger trial has more aggressive therapy with an autotransplant. The elderly study obviously does not, but again irrespective, patients with more aggressive disease do worse.



Slide 21: Upfront Use of Small Molecules

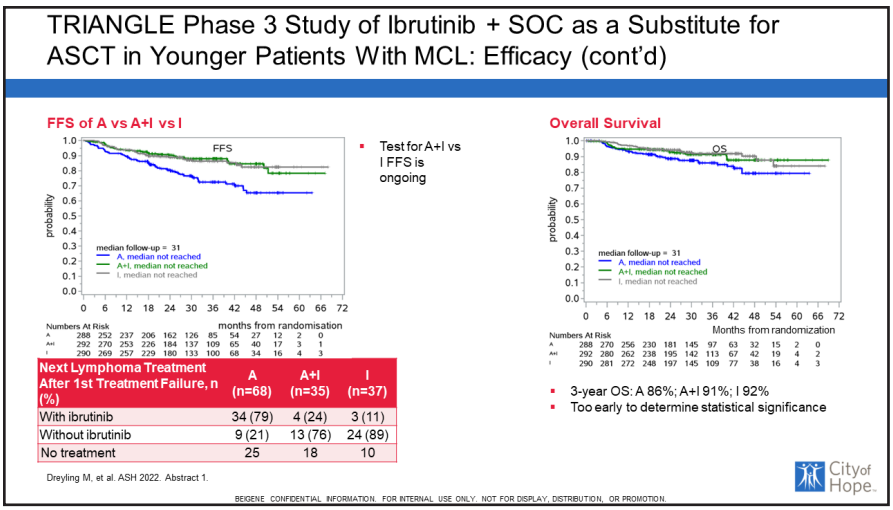
This has led to moving up some of these small molecules. We already discussed the SHINE trial was looked at adding ibrutinib to bendamustine and rituximab. Part of this may be due to the patient population. Obviously, older patients tend to not tolerate combinations as much, a reason why we don't necessarily recommend very intensive therapies for these patients but for the younger patients or other ones, BTK inhibitors seem to make a difference as these are generally the drugs that we typically use most. It has really been the drugs that have made the biggest difference in clinical outcomes over the last 10 years.



Slide 22: TRIANGLE Phase 3 Study of Ibrutinib + SOC as a Substitute for ASCT in Younger Patients With MCL: Study Design and Patients

Recently there was a TRIANGLE trial, which is a bit more complicated than SHINE, but if you think about this trial and look at it, there were 3 arms randomized one-to-one. Again, these were patients who were considered to be eligible for high-dose chemotherapy and an autotransplant. These patients were either randomized to what the German standard treatment was in the MCL Younger trial, R-CHOP, alternate with R-DHAP, followed by an autotransplant, and then you had experimental Arm 1, which added R-CHOP plus ibrutinib, alternate with R-DHAP, followed by an autotransplant, and then 2 years of ibrutinib maintenance.

Then you had Arm 2, the experimental Arm 2, which looked at R-CHOP plus ibrutinib, R-DHAP alternating, and then 2 years of ibrutinib maintenance without the inclusion of autologous stem cell transplantation. As the LYMA trial published their information as this trial was ongoing, all the arms had R-maintenance added to them when that information was present. When they published this information, it appeared that there was equal distribution of R-maintenance in all 3 arms.

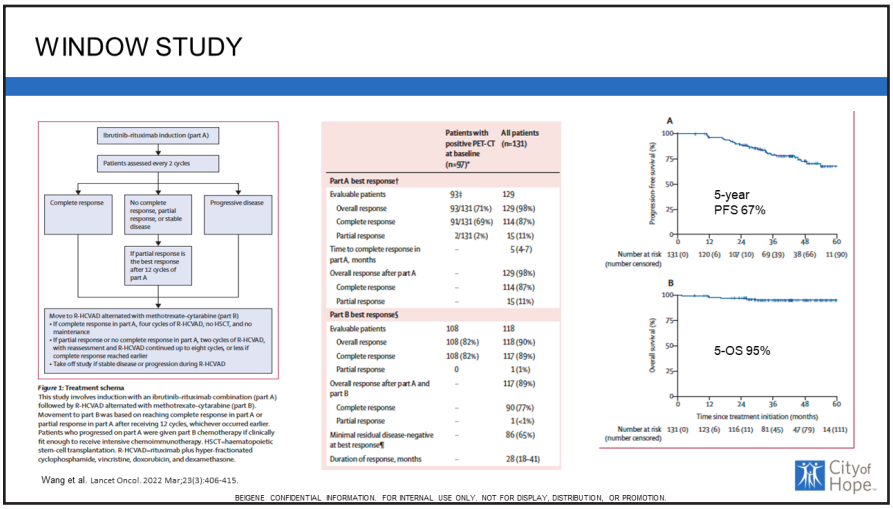


Slide 23: TRIANGLE Phase 3 Study of Ibrutinib + SOC as a Substitute for ASCT in Younger Patients With MCL: Efficacy (cont'd)

The key takeaway from this trial was that it appeared that there was no benefit to autologous stem cell transplantation. As the 2 experimental arms had overlapping failure-free survival curves and were better than the

arm that did not include ibrutinib for maintenance. A key point to remember is that at least early on, this is not a very long follow-up for this trial. It's only about 33 months. We're also still waiting for the official publication of this article, so we can get more in-depth information from this. Based on this abstract, I know some institutions around the US have implemented the TRIANGLE as their standard of care and I do know the Germans have implemented it as their standard of care.

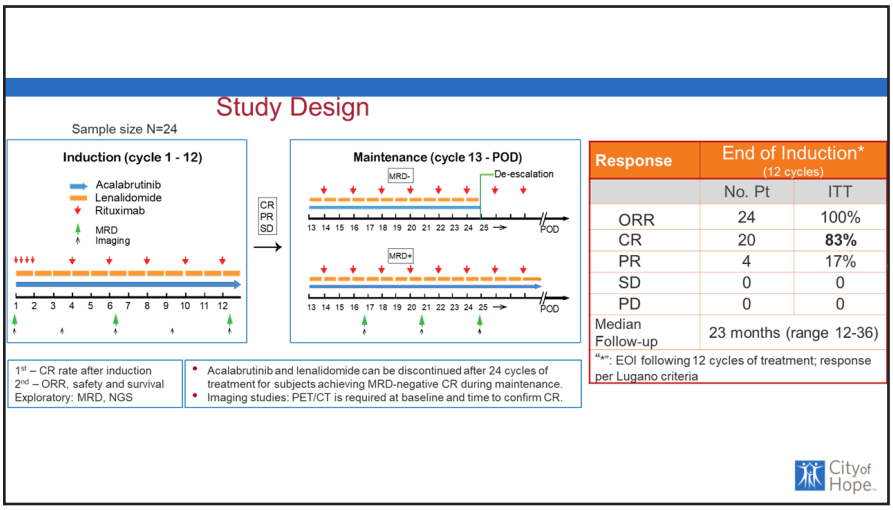
If you look at the curve to the right, as of right now, there is not an overall survival benefit with this regimen, so we still need to get more information as this trial further matures.



Slide 24: WINDOW STUDY

The next study is, that I'm sure a lot of you are aware, was the WINDOWS trial. This was a study from Dr. Michael Wang and MD Anderson. This study gave patients a duration of R-Hyper CVAD chemotherapy based on response to the initial therapy. As you can see from this initial treatment, patients had a very high progression-free survival, 67% in 5 years, very high overall survival.

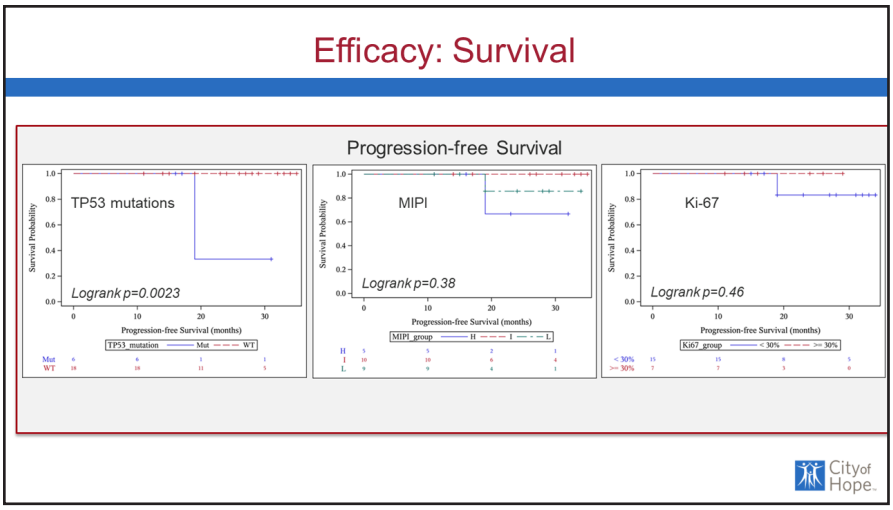
As you look at the curve to the left, there was a very high overall response rate during the initial ibrutinib and rituximab arm, a little bit less when patients were consolidated with R-Hyper CVAD, as I assume, some of these patients had some loss of response. A very early look at a potentially chemo-free induction regimen, even though there was consolidation with chemotherapy after the year of ibrutinib and rituximab.



Slide 25: Study Design

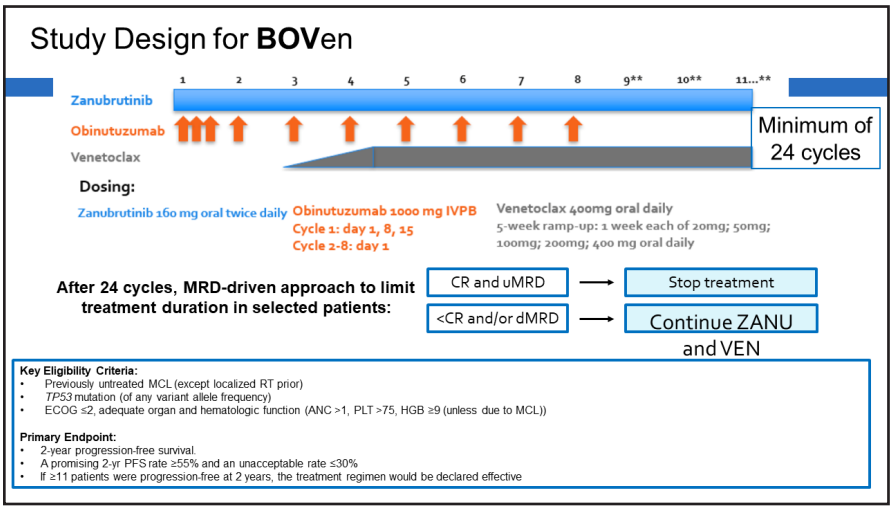
From that we've had multiple other treatment regimens trying to add to this. This is a study from the Cornell Group which added acalabrutinib to lenalidomide (Revlimid®) and rituximab. These were given for the initial 12 cycles.

After 12 cycles, patients would then go into what we consider maintenance. After 24 cycles, the patients were in a minimal residual disease (MRD) undetectable state by the adaptive clonoSEQ Assay. These patients had the option of stopping all therapy after 24 months, whereas those who are MRD positive will continue treatment as a maintenance regimen. As you can see to the right, the overall response rate in the 24 patients was 100%. 83% complete response rate as 20 of the 24 patients had a complete response. Median follow-up is a little bit less than 2 years in this trial.



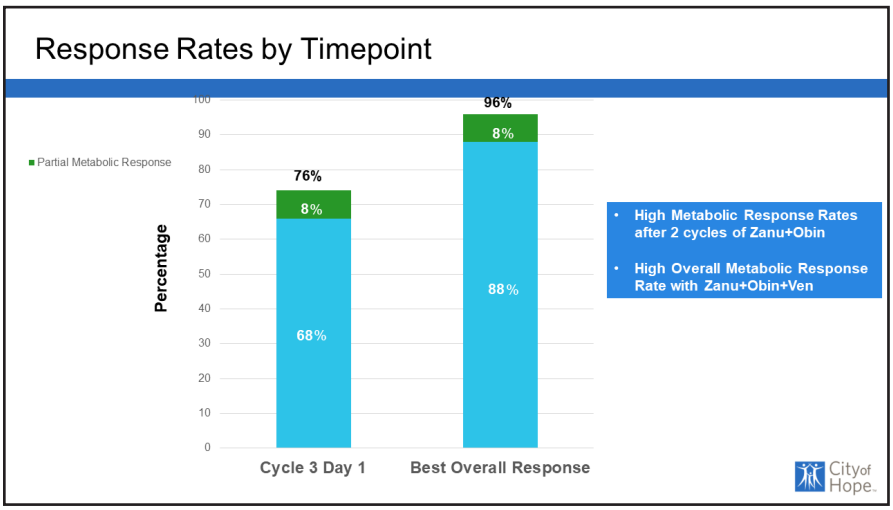
Slide 26: Efficacy: Survival

Now, if you look at some of the higher risk characteristics that we discussed before, it appears at least based on MIPI score, patients with high-risk MIPI had worse outcomes than those with low and intermediate. Ki-67 again appeared to trend toward worse with those with high Ki-67, 30%, but neither of these 2 are statistically significant as you see the *P* values at 0.38 and 0.46. Patients with p53 mutations appear to not necessarily benefit from this regimen as those who were p53 unmutated. As you see, the *P* value is significant at 0.0023 for that high-risk patient population, suggesting that we probably do need to do a little bit more to improve outcomes in that patient population.



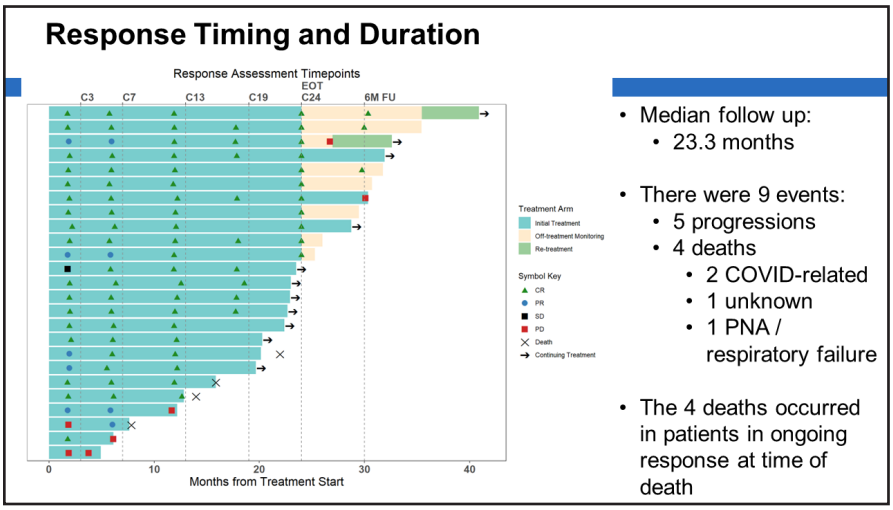
Slide 27: Study Design for BOVen

This group at MSK (Memorial Sloan Kettering Cancer Center) has looked at a novel regimen called BOVen. This is using zanubrutinib (Brukinsa®), obinutuzumab (Gazyva®), which is another CD20 antibody, and venetoclax (Venclexta®). These patients initially start off with zanubrutinib and obinutuzumab and then after 3 cycles, patients are allowed to ramp up venetoclax from 20 milligrams up to 50, 100, 200, and 400. This is a weekly ramp-up. They can continue on 400 milligrams daily in conjunction with zanubrutinib. These patients were given this treatment for a minimum of 24 cycles. Very similar to the study from acalabrutinib, lenalidomide, and rituximab from Cornell. After 24 cycles, these patients would have the option of stopping treatment; for those with less than a complete response or had detectable minimal residual disease by the adaptive clonoSEQ Assay, they can continue zanubrutinib and venetoclax. This study specifically was looking for patients with p53 mutations of any variant allele in frequency. They initially started with molecular assay, but they did also subsequently change their protocol to allow patients with high expression by IHC to be enrolled into the trial.



Slide 28: Response Rates by Timepoint

If you look at the response assessment, the early response assessment before the addition of the venetoclax shows an overall response rate of 76% with a complete response rate of 68%. The best overall response, including all 3 agents, shows an overall response rate of 96% and a complete response rate of 88%, a very high response rate in this patient population.

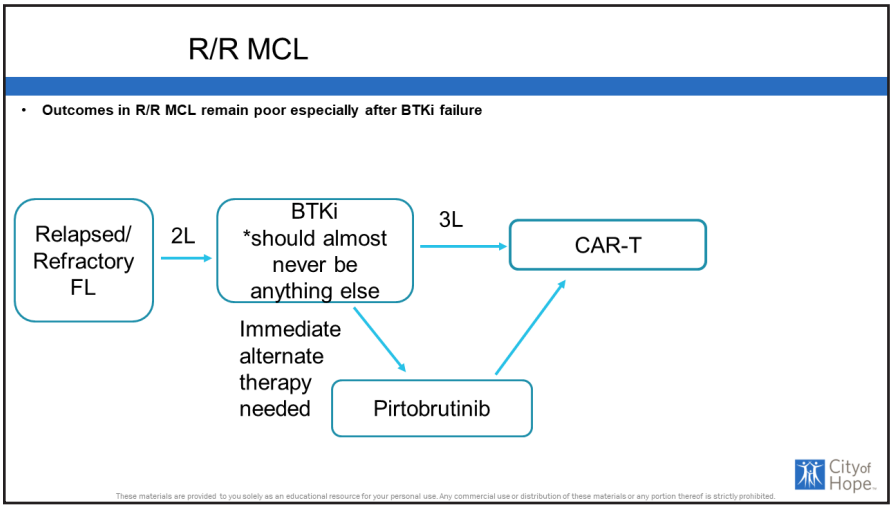


Slide 29: Response Timing and Duration

If you can look at this swimmer's plot in the median follow-up, a little less than 2 years, majority of these patients were still in response. There were 9 events on the trial. Five patients had disease progression. There were 4 deaths related to COVID, one unknown and one of pneumonia. The 4 deaths noted were in patients who were in ongoing response. Of the 20 patients that were enrolled in this initial cohort, 15 of the patients continued to still be in response at last follow-up.

The bigger thing about this, these were p53 mutated patients. As we've seen from the other curves, these patients tend to have a very poor outcomes overall when they're treated with chemoimmunotherapy. A lot of these patients will get a response to chemoimmunotherapy, but the problem is that responses aren't durable as a lot of these patients will relapse within 12 to 24 months of the receipt of chemotherapy, irrespective of use of an autologous stem cell transplantation.

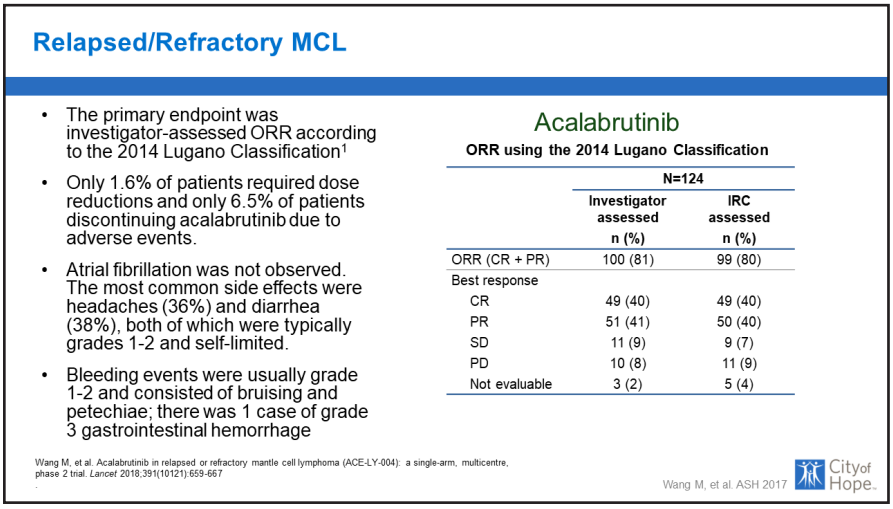
If we look to this, to the right, there are a fair number of patients on this regimen who probably have potentially stopped therapy who are still in response on this BOVen regimen. We will wait to see further follow-up of this regimen to see how durable the responses are for these patients.



Slide 30: R/R MCL

Switching over before we wrap up to relapsed/refractory mantle cell lymphoma. For the most part, relapsed/refractory mantle cell lymphoma, the bedrock of therapy, if you have not received a BTK in the first-line setting, you should more than likely get a BTK in the second-line setting.

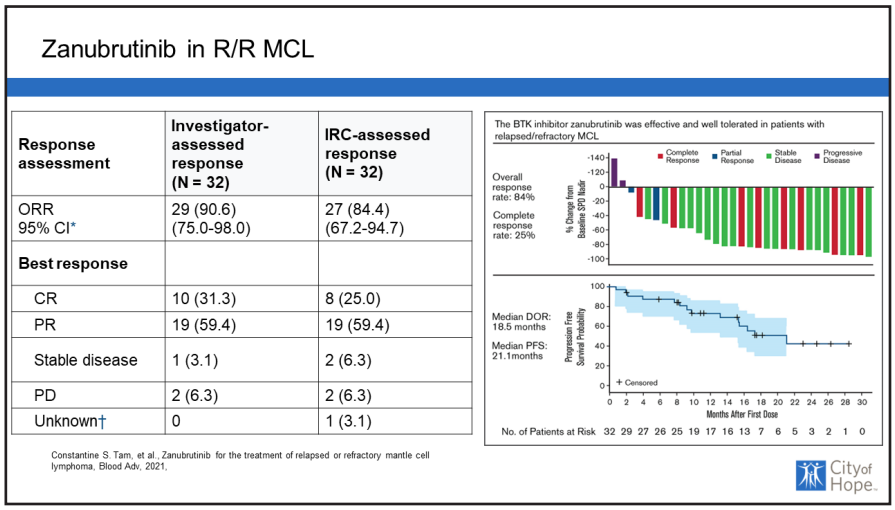
We know from retrospective data that there's still a high use of chemotherapy in second-line mantle cell lymphoma. That should not be the case, as all of the data suggests that your responses to BTK inhibitor are better if you get in second-line versus third-line or later. BTK inhibitors appear to have better durability of response compared to giving second-line chemoimmunotherapy. Again, unless there is a viable reason for you not to get a BTK inhibitor in the second-line setting, you should be getting a BTK inhibitor.



Slide 31: Relapsed/Refractory MCL

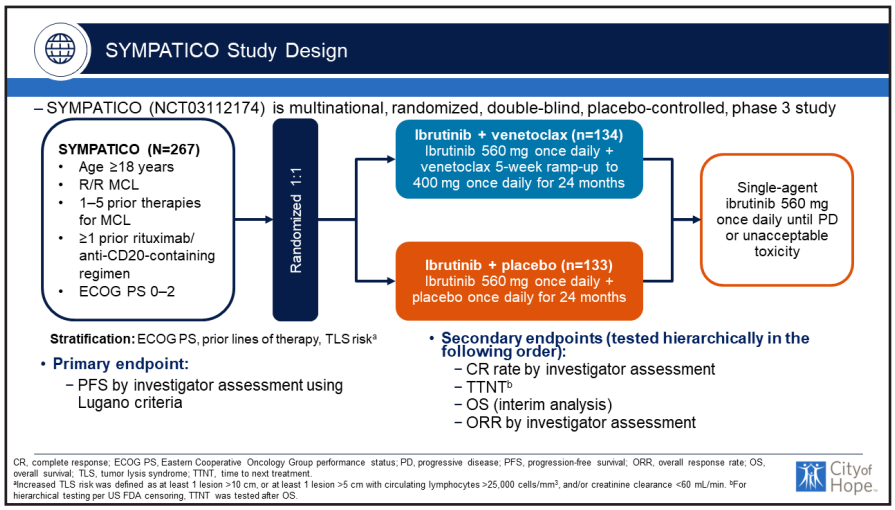
The options in a second-line setting for a BTK inhibitor are calabrutinib and zanubrutinib, for third-line and beyond, we have CAR T (CAR T-cell Therapy), but also we have the non-covalent inhibitor pirtobrutinib (Jaypirca®), which we will discuss. Just to quickly summarize, acalabrutinib was approved on a study from Dr. Michael Wang, published in 2018. As you see a very high overall response rate in a relapsed/refractory setting.

This is a little bit different from the population that received ibrutinib, as all of these patients were second-line patients. You do see a high response rate, high CR rate, and this is durability of response in this patient population. At least very early on, the AE (adverse effects) profile of acalabrutinib appeared to be better than what we saw with ibrutinib. As you see less rates of atrial fibrillation, less rates of bleeding, arthralgias, myalgias, and rash, given that acalabrutinib has more fidelity to BTK than ibrutinib did.



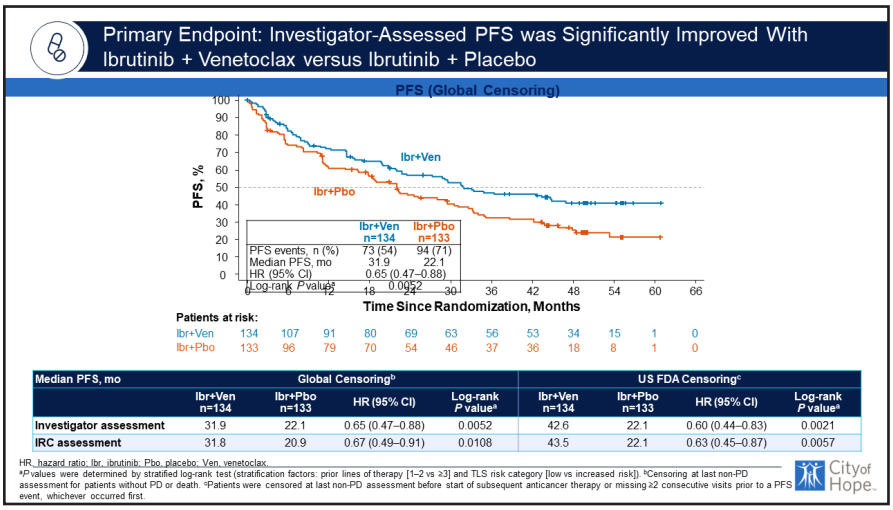
Slide 32: Zanubrutinib in R/R MCL

Next we have zanubrutinib, which was initially studied in a population coming out of China, but there was a US-Australia study that also looked at zanubrutinib. Again, 32 patients, very high overall response rate, high complete response rate. As you can see, a very impressive duration of response of 18.5 months in PFS of 21.1 months. A better safety profile than what we saw with ibrutinib in this patient population. These 2 drugs are available in the second-line setting. Ibrutinib is no longer available due to, unfortunately, the data that came from the SHINE trial.



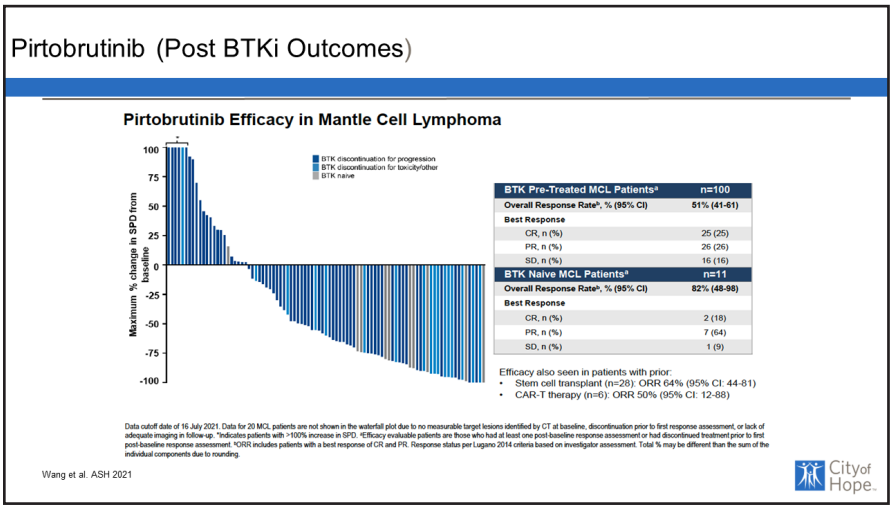
Slide 33: SYMPATICO Study Design

More recently we had the SYMPATICO study, which was ongoing before ibrutinib lost its indication in mantle cell lymphoma, a randomized trial of ibrutinib + venetoclax versus ibrutinib + placebo, one-to-one randomization, and in 267 patients. Patients will continue the combination for 24 months. Thereafter, they would stay on single-agent ibrutinib until toxicity or disease progression. This study showed that there was a benefit of this combination of a substantial progression-free survival benefit. As you see in the PFS events, about 21 less than in the ibrutinib placebo arm, the median PFS of 31.9 months versus 22.1 months so an improvement around 9 months, suggesting a benefit of the combination.



Slide 34: Primary Endpoint: Investigator-Assessed PFS was Significantly Improved With Ibrutinib + Venetoclax versus Ibrutinib + Placebo

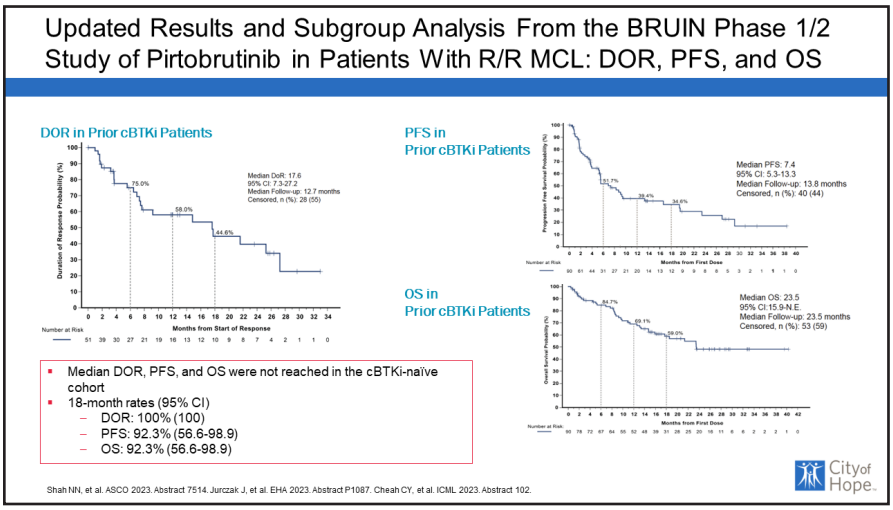
The issue we have right now is ibrutinib no longer has an indication. Some have suggested substituting a second-generation BTK inhibitor of venetoclax in this patient population. There is data, as we saw with BOVen, with zanubrutinib and venetoclax, and there's data from an upfront trial with acalabrutinib and venetoclax showing that both of these are both also safe with venetoclax. Although, this issue will come down to insurance approval based on these were not the agents studied in this patient population.



Slide 35: Pirtobrutinib (Post BTKi Outcomes)

Pirtobrutinib is the non-covalent BTK inhibitor. I'm sure a lot of you have discussed this information about this trial. This is the majority of patients who had failed a covalent BTK inhibitor, but there are also some patients who are on this trial who had stopped the BTK inhibitor for intolerance - of those a hundred patients, but 100 patients with an overall response rate of 51%, complete response rate of 25%, partial response rate, obviously of 26% in this patient population.

As you can see from the waterfall plot, there is again a high number of these patients with a response. More importantly, the 11 patients who are BTK naive, you see an overall response rate of 82% with a complete response rate of 18%. This has subsequently improved with longer follow-up, suggesting that this is also a very effective agent in BTK naive patients and at least early on appears to have a better toxicity profile than what we see with some of the covalent drugs.

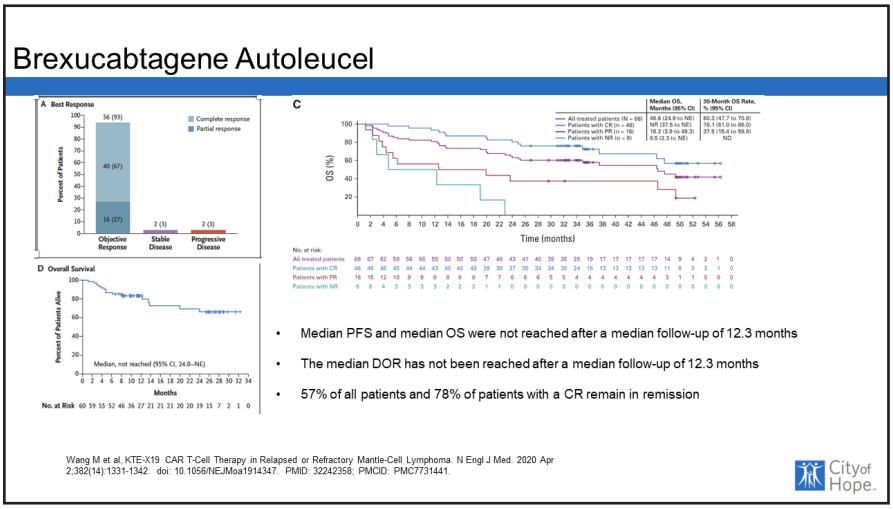


Slide 36: Updated Results and Subgroup Analysis from the BRUIN Phase 1/2 Study of Pirtobrutinib in Patients With R/R MCL: DOR, PFS, and OS

This next slide I show you, just to be aware, if you look after 6 months, there are very few patients who are still on pirtobrutinib. The point of bringing this up is that we don't really think of pirtobrutinib as a very effective therapy post-covalent BTK inhibitor. It may cause us some response, but these responses will more than likely be durable. The vast majority of these patients, I would suspect on this duration of response curve, are patients who stopped a previous covalent BTK inhibitor for intolerance, not for progression.

As the median duration of response for intolerant patients was not reached in a clinical trial, and it was much shorter for patients who had a covalent BTK inhibitor, especially those whose most recent treatment before going on this study was a covalent BTK inhibitor. So pirtobrutinib, for all we know, is a treatment that can bridge us to something else that is more durable in patients with mantle cell lymphoma.

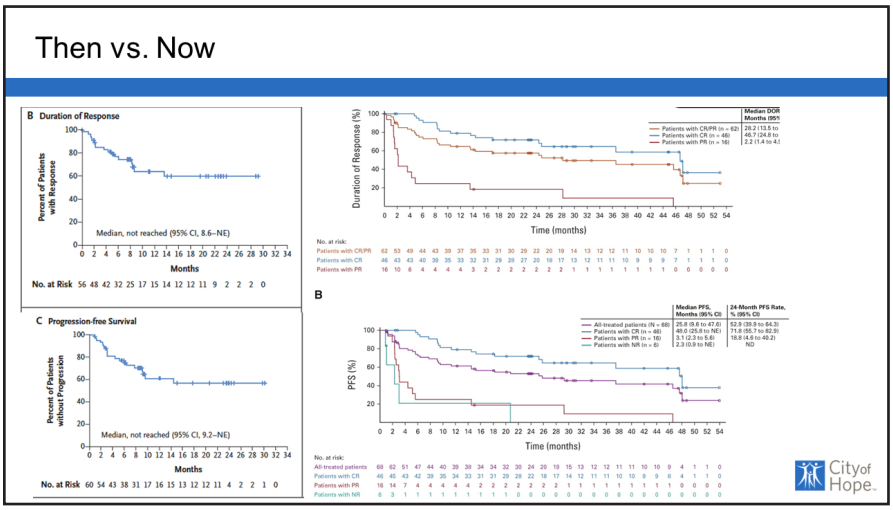
Unlike CLL, mantle cell lymphoma does not have a BTK binding site mutation as a reason for progression on a covalent BTK inhibitor. Having a non-covalent BTK inhibitor is not necessarily going to overcome the resistant mechanisms that we see in mantle cell lymphoma. Pirtobrutinib may be better positioned as a second-line drug than as where it is right now as a drug given after a covalent BTK inhibitor.



Slide 37: Brexucabtagene Autoleucel

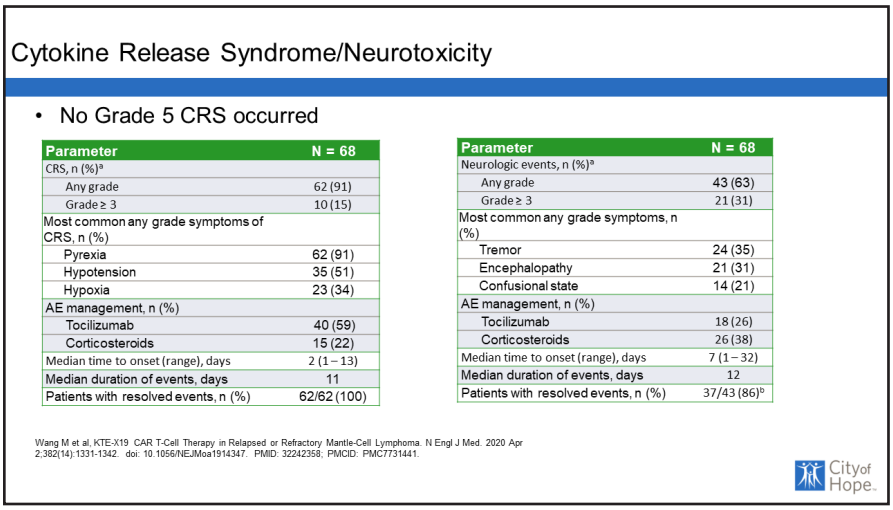
Lastly, before we wrap up, we'll start talking about some T cell-directed therapies. I'm sure a lot of you are aware of brexucabtagene autoleucel (Tecartus®), which is a CAR T product. This was a game changer in the sense that this was a post-BTK patient population, and it indicated responses that we had not seen, overall response rate 93%, complete response rate 67%. Very early on, it appeared that the median duration of response, progression-free survival and overall survival had no median at the initial presentation. Unfortunately, with more follow-up, what we have seen obviously is that these curves continued to drop.

It does not appear that CAR T is curative in mantle cell lymphoma, like what we see in diffuse large B-cell lymphoma. As you can see with the subsequent Kaplan-Meier curves, duration of response had a plateau at the subsequent 3-year follow-up, you see that this has continued to drop. Every time we get an update and report of patients with mantle cell lymphoma and brexu-cel, I suspect we'll continue to see these curves drop further and further.



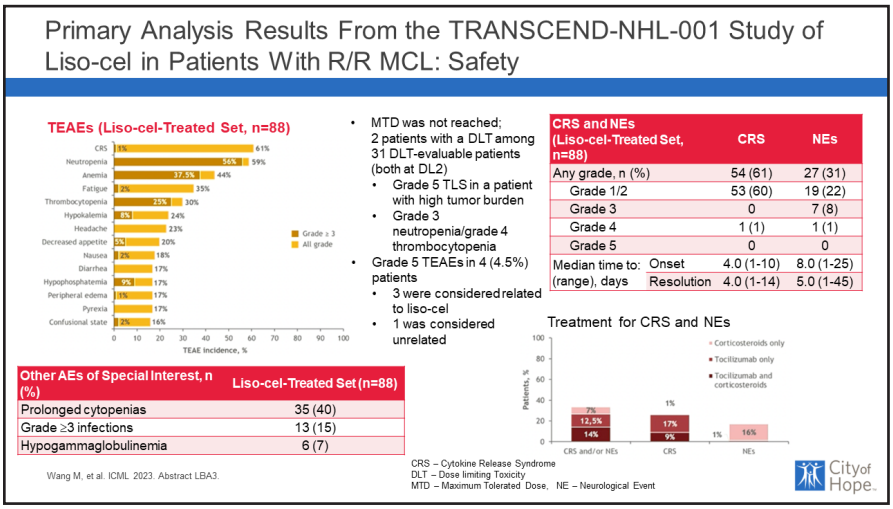
Slide 38: Then vs. Now

We may be lucky that there may be a small cohort of patients who may potentially get a cure, but the numbers of patients who potentially could be cured from this treatment will be nowhere near what we can see in large cell lymphoma, suggesting that we will still need further treatment options post brexu-cel. Additionally, some of the issues with brexucabtagene autoleucel is side effect profile. Cytokine release syndrome (CRS) is something we expect with T cell-directed therapy and as you see, 91% of the patients had CRS with 15% of the patients with Grade 3 or above.



Slide 39: Cytokine Release Syndrome/Neurotoxicity

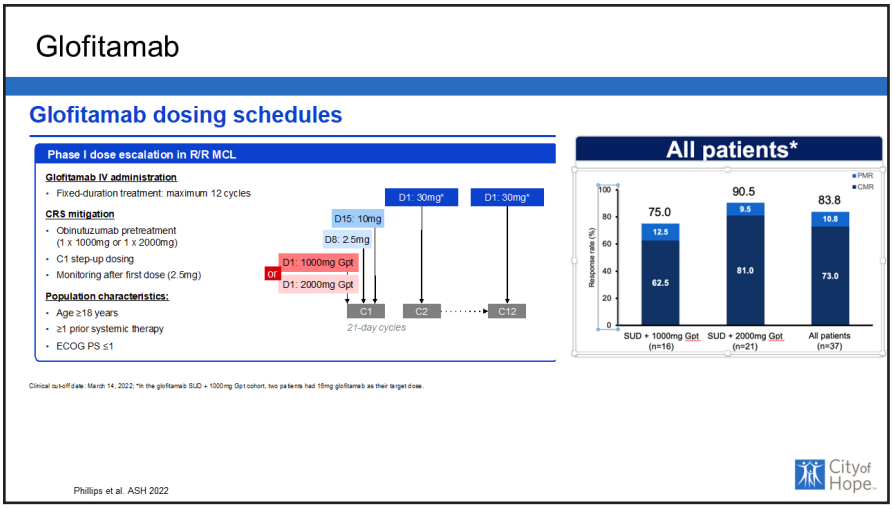
The bigger concern with brexucabtagene autoleucel is really the neurological toxicity or ICANS (Immune Effector Cell-Associated Neurotoxicity Syndrome). As you can see, Grade 3 or above neurological events occurred in 31% of the patients. This information has also been replicated in a real-world dataset, suggesting that there is a bit of a concern with the toxicity with brexu-cel in this patient population. Now, we don't have another better option available to us right now, but this is something that should be discussed with patients before we receive brexucabtagene autoleucel, is that the high-risk concern about ICANS and neurological events because unfortunately some of these events are irreversible.



Slide 40: Primary Analysis Results From the TRANSCEND-NHL-001 Study of Liso-cel in Patients With R/R MCL: Safety

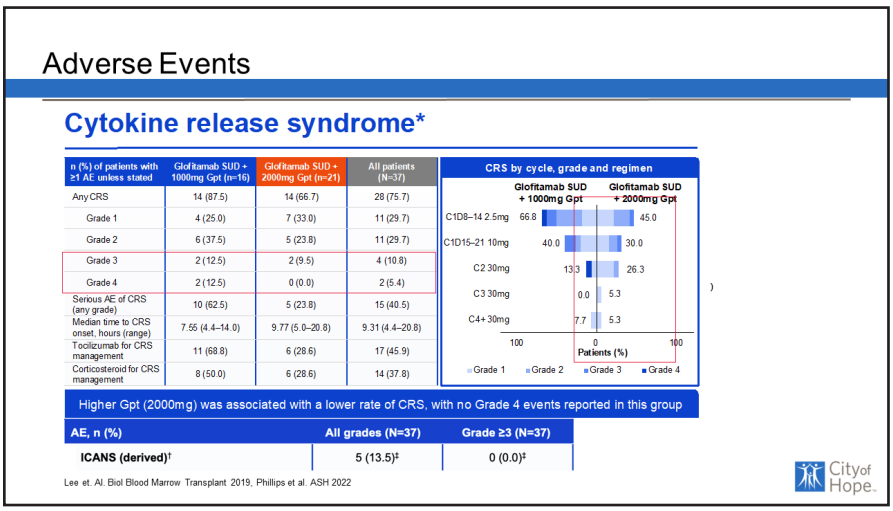
To that end, there is data looking at Liso-cel (lisocabtagene maraleucel/Breyanzi®). I didn't include the progression-free survival and response curves because I think the biggest thing we took from the Liso-cel presentation is if you can look at the neurological events. The Grade 3 or above neurological events was 9% compared to 30% with brexucabtagene autoleucel, suggesting that because of the co-stimulatory domain difference between these 2 products, Liso-cel appears to be a much safer product and will likely be the preferred agent if this drug does get FDA approval for patients with mantle cell lymphoma.

Unless there is something that plays out with long-term fault, this suggests that there is really a significant efficacy difference, because the difference between 30% and 9% is substantial in this patient population, given as I mentioned before, unfortunately ICANS can be something that is not reversible. Before I wrap it up, we will just talk about bispecific antibodies.



Slide 41: Glofitamab

To date, glofitamab is the only bispecific antibody with any substantial data in patients with mantle cell lymphoma. Similar to all bispecifics given in a step-up dosing fashion, patients will get 2.5 milligrams, 10 milligrams, and 30 milligrams. Unlike what they do in large cell lymphoma, glofitamab is preceded by 2000 milligrams of obinutuzumab. This is given over 2 days, day -7, day -6 with glofitamab starting on cycle day 1. As you can see to the right in this early data set, the 37 patients, a high overall response rate of 83.8%, complete response rate of 73%.

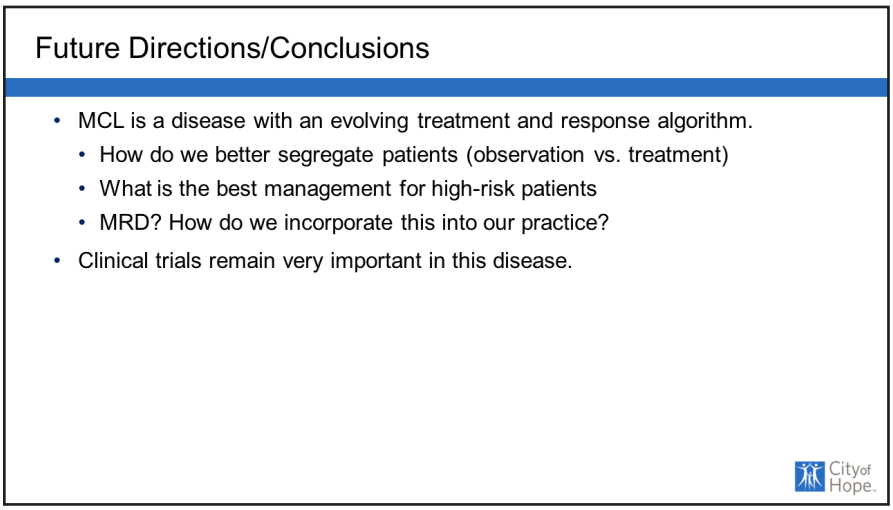


Slide 42: Adverse Events

I think focusing on the adverse event profile, cytokine release syndrome was higher than what we see in other disease subsets, 76% majority of these were Grade 1 and Grade 2. We did see the reduction in Grade 3 or above with the addition of the 2000 grams (milligrams) of obinutuzumab, which is why that is utilized moving forward.

There was no Grade 3 or above ICANS events. Only one patient had a Grade 1 ICANS with the 2000 milligrams of glofitamab, suggesting less neurological complications in this patient population with this treatment.

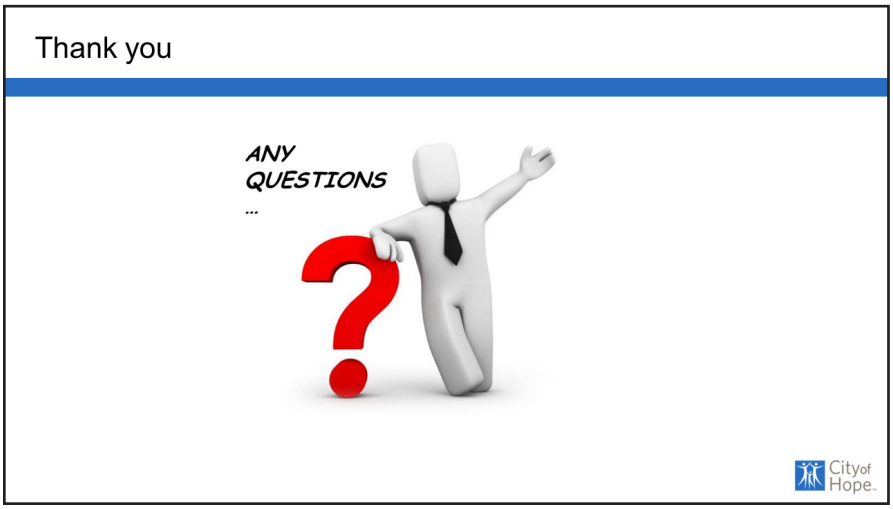
At this point, the response assessment to glofitamab is immature. We cannot compare directly to CAR T. This is something we're going to have to wait for more robust and mature information to come out in the next couple years.



Slide 43: Future Directions/Conclusions

With that, I'll conclude. Mantle cell lymphoma is a disease, it is evolving, but things are changing for the better for patients. As we move forward, how do we better segregate patients with observation versus treatment? How do we best manage high-risk patients? I didn't really discuss a lot about minimal residual disease, but how do we incorporate that into our clinical practice now that clonoSEQ has an FDA approval? How often will insurance actually pay for this and allow us to track these patients?

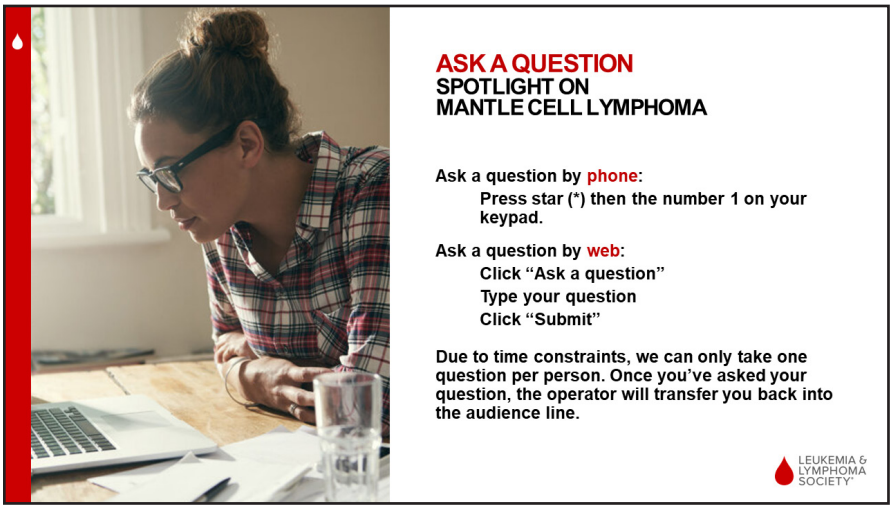
To emphasize, clinical trials remain very important in this disease subset. If you are in a practice that has a clinical trial that is available for you, that is something to strongly consider, as the only way we're going to continue to improve outcomes and how we've made such substantial improvements in outcomes of patients with mantle cell lymphoma is clinical trials, which are offering generally treatments that we can't give you as a standard of care and have shown very encouraging promise in other subsets. With that, I will open up for questions.



Slide 44: Thank you

Lizette Figueroa-Rivera:

Thank you so much for this information Dr. Phillips and for showing us how all of these studies have really shaped our current therapies.



Slide 45: ASK A QUESTION

Lizette Figueroa-Rivera:

We'll take our first question from the web audience. Eric is asking: Is there anything improving overall survival for younger fit patients or is everything right now just improving PFS, progression-free survival?

Dr. Tycel Phillips:

Yes. Unfortunately, none of our trials have shown an overall survival benefit with any treatment. I think as a lot of us have researched mantle cell lymphoma, overall survival we know has improved and it probably just improved because of the integration of all these treatments we've talked about and sequentially staggering out, which will allow patients to live longer. Unfortunately, like I said, other than allogeneic stem cell transplantation, we don't really have a true curative treatment. So far, none of the randomized trials have shown an overall survival benefit to any of those novel treatments that we're implementing. We have improvements of failure-free survival and progression-free survival, which we hope will allow patients to live longer but an overall survival benefit has not been shown in any of the trials.

Lizette Figueroa-Rivera:

We'll take the next question from our telephone audience, please.

Operator:

The next question comes from Karen.

Karen:

I am 76 years old. I was diagnosed with mantle cell lymphoma back in 2022. I have had chemotherapy and I have had CAR T-cell therapy. My question is: What else is up for me to have now for survival or what would be my survival rate?

Dr. Tycel Phillips:

Without knowing all the specifics, typically if a patient proceeds to CAR T very early, most physicians would probably suspect you have more aggressive disease unless that was given as part of a clinical trial. Again, the BTK inhibitors are there in case you have not received a BTK inhibitor and those drugs are still effective. They tend to be more effective in those in early lines of therapy and depending on certain mutation or morphologic features, the drugs do seem to work a little bit less effective in those with blastoid/pleomorphic or those with p53 mutations.

Ideally in a situation such as failure of CAR T, we don't necessarily know for sure because we don't have a lot of trials that have looked into post-CAR T space. Depending on what type of response you had to CAR T, if they can get you a bispecific antibody, that is something that can be considered or alternatively, they can revert back again, depending on clinical features, to other drugs, such as chemoimmunotherapy. There's still Velcade. There's lenalidomide. There are other drugs that can be tried in this situation if a patient would have relapsed after CAR T.

Lizette Figueroa-Rivera:

Our next question Doctor, Blair asks: In a relapse from frontline treatment of mantle cell lymphoma, is it possible that the relapse takes the form of another cancer, such as follicular lymphoma?

Dr. Tycel Phillips:

So generally not. I know there has been some question of mantle cell transforming, but it pretty much is a more aggressive mantle cell lymphoma. Mantle cell should not change to another form of non-Hodgkin's lymphoma. Mantle cell doesn't become diffuse large B-cell lymphoma, it doesn't become follicular lymphoma. If there's a diagnosis of an alternative lymphoma, then that alternative lymphoma was probably already present. It has no relation to the mantle cell lymphoma.

Lizette Figueroa-Rivera:

Lisa is asking: For recurring mantle cell lymphoma, how many times can you participate in a CAR T-cell trial?

Dr. Tycel Phillips:

Standard of care - once. Obviously, there are clinical trials that are looking at CAR Ts with other targets or having dual targets. A lot of those trials will take patients who have already failed brexucabtagene autoleucel. As far as standard of care, you can only get it once.

Operator:

Our next question comes from Francis. Francis, your line is now open.

Francis:

What medications do you use for relapse?

Dr. Tycel Phillips:

If it's an initial relapse as a frontline therapy, generally it would be either zanubrutinib or acalabrutinib. Depending on some of the risk factors, if it's a patient who has a p53 mutation or blast or pleomorphic variant, those would probably be the patients that you can consider treating with a SYMPATICO regimen, which adds venetoclax just because that did show an advantage over single-agent BTK inhibitors in those patient populations. Patients who have p53 mutations specifically, if I start them on the BTK inhibitors, I will likely get them approved for a CAR T drug. Not to say that I will stop the BTK inhibitor, but we do know the BTK inhibitors do not have durable responses in p53-mutated patients. Again, getting the CAR Ts approved and set up is just me anticipating the relapse that is likely to happen within a year.

Lizette Figueroa-Rivera:

The next question Doctor comes from Michael. Michael is asking: Has mantle cell lymphoma become more common? When I was diagnosed back in 2013, my oncologist was my only source of solid information. Now I see a lot of references to it.

Dr. Tycel Phillips:

I don't think it's become more common. I do think some patients with mantle cell lymphoma, at least before, were misdiagnosed with other forms of non-Hodgkin's lymphoma. I do think there's a lot more research in mantle cell lymphoma thanks to organizations like the LLS (Leukemia & Lymphoma Society) and LRF (Lymphoma Research Foundation) and because of that there's been improvements in a lot of the knowledge base and what makes mantle cell lymphoma tick. Hopefully, we can continue to divert research into this area because I think all our hope is that we can eventually cure mantle cell lymphoma, or at the very least, we can accomplish what we consider a functional cure, which means that patients live with this disease but they will eventually die from something else.

Lizette Figueroa-Rivera:

We'll take the next question from our phone audience.

Operator:

Our next question comes from Carol. Carol, your line is now open.

Carol:

What is the record of effectiveness in the use of BRUKINSA® as a maintenance drug?

Dr. Tycel Phillips:

BRUKINSA® in and of itself has not been studied like ibrutinib. All of the data we have for a BTK maintenance has come from the use of ibrutinib. It was a TRIANGLE study. There was also a trial that came out of Northwestern that looked at a BTK maintenance, all suggesting a progression-free survival benefit. The studies that I use in BRUKINSA have always just continued to BRUKINSA or zanubrutinib after initial start. We don't really know how that will work as a maintenance, but I would suspect that it wouldn't be any difference in ibrutinib because we don't suspect that there is much of a clinical difference between the 3 covalent BTK inhibitors.

Lizette Figueroa-Rivera:

Sherilyn is asking: I had CAR T-cell therapy. How long is CAR T supposed to last?

Dr. Tycel Phillips:

We don't know for sure. I think we are still learning. As I pointed out with the ZUMA-2 update, we do know that with a 3-year follow up, there were quite a few progressions than what the initial presentation has. With the real-world data set, they have shown that there is continual relapses. Some people are reporting relapses even after 5 years. I think the median duration of response and progression-free survival is still ongoing.

As these patients continue to relapse, we'll eventually get to a point where we'll get a true median, but we hope that any patient that gets CAR T will have at least several years of remission, but some people unfortunately have relapses much sooner than that and some people are lucky enough to have 5 years or more.

Lizette Figueroa-Rivera:

Sue is asking about MRD. I know you mentioned minimal residual disease and how that testing affects treatment.

Dr. Tycel Phillips:

As of right now, MRD has really been something that we've only really utilized in clinical trials. There are a couple of ways of evaluating minimal residual disease. How I like to tell my patients is, if you look at an iceberg in the water, the water level is what we see with imaging PET scan, and anything below the water is what the PET scan/CT can't detect, and that's why MRD can help us out. The clonoSEQ Assay is what we typically use here in the US. It has a sensitivity of 10 to the negative 6 (10^{-6}), so it can basically detect anything within a million cells.

Our clinical recess has shown that patients who are MRD undetectable, and that 10 to the negative 6 (10^{-6}) tend to have longer progression-free survivals. I don't think we've really fully realized the potential of this test and whether maybe we can intervene early if patients who regain MRD positivity, and we can get these patients back into remission. I think there's a lot of different ways that eventually this test will help make lives better for patients with mantle cell lymphoma, but as of right now it's really just integrated into clinical trials, even though as I mentioned, it does have an FDA approval now, so we can check but we really can't do anything with the test other than provide that information today.

Lizette Figueroa-Rivera:

We'll take the next question from our telephone audience, please.

Operator:

Our next question comes from Papo. Go ahead. Your line is open.

Papo:

At one point you talked about a German study with regard to, I believe it was IMBRUVICA, which I am on. You said they stopped it because they weren't showing any benefit to it. Is that what you meant to say? Or is that what you were saying? There hasn't been improvement or is it worth keeping going with the dosage for the 3 years that I've been [on it]?

Dr. Tycel Phillips:

The study was the SHINE trial. It was a frontline trial, so it wasn't a relapsed/refractory trial. A full FDA approval of ibrutinib was tied to this frontline trial which randomized patients to ibrutinib versus BR (bendamustine + rituximab). That study actually did not show a survival benefit and had some concern about toxicity from the experimental arm, which led to the company withdrawing the indication. The German study is a TRIANGLE study which was for patients in the frontline setting, but those who are considered to be eligible for stem cell transplant.

That study suggested that there was no benefit to the use of autologous stem cell transplantation and patients benefited from 2 years of ibrutinib maintenance. Again, that study has led to the adoption of that regimen as the standard frontline therapy in Germany and some in the US have adopted that as a frontline therapy. For your situation, if you are tolerating the ibrutinib and you have no adverse events, most people would continue to keep you on that medication because we do know ibrutinib is effective in a relapsed/refractory setting. It is just, unfortunately, not available for new people to start because of the SHINE data which led to loss of approval.

Lizette Figueroa-Rivera:

The last question today comes from T. T is asking: Can an indolent mantle cell lymphoma never develop to a form of cancer that needs any treatment and remains indolent or slow growing for decades?

Dr. Tycel Phillips:

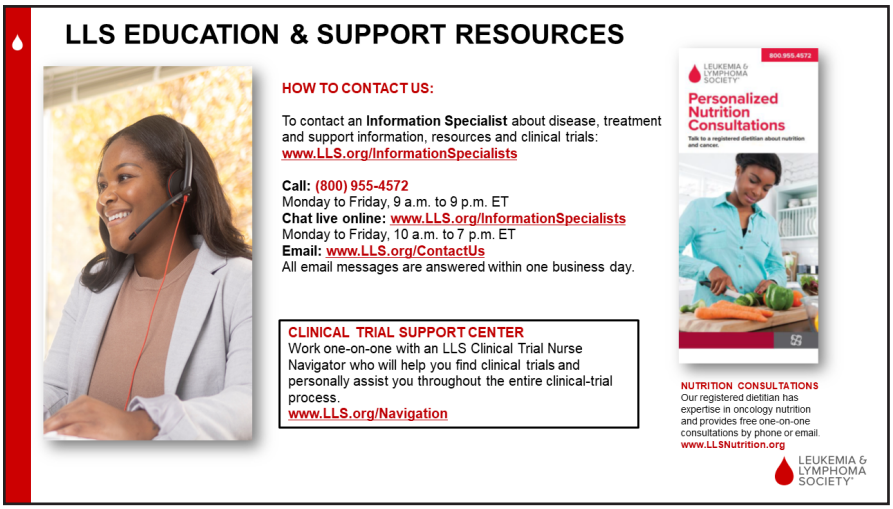
I would suspect yes. I think we are really still trying to figure that out. I don't know if you remember in the beginning, everybody with mantle cell lymphoma historically was treated. What we are trying to start to see now, there are patients 20 to 30 years out who got an initial treatment with chemo and an autotransplant that are still in remission

now. A lot of these patients probably did not require treatment at the time of being treated. We're trying to figure out these long remission patients.

Is it the chemo or is it just the disease in itself? Which again, we treated just because we thought we needed to treat. That has just allowed these patients to remain in long-term remission. I would suspect that patients who have truly indolent mantle cell lymphoma, yes, they can probably live decades with this disease and not need treatment. These are the patients who likely, even if they do require treatment, will be the functional cures, meaning patients who probably die of natural causes versus dying of the mantle cell lymphoma.

Lizette Figueroa-Rivera:

Thank you T for that question which was our final question today and special thanks to you Dr. Phillips for volunteering your time and expertise with us today.



Slide 46: LLS EDUCATION & SUPPORT RESOURCES

If we weren't able to get to your question or you'd want more information or resources, you may speak to an LLS Information Specialist at 1-800-955-4572 from 9:00 AM to 9:00 PM Eastern Time or reach us by email at LLS.org/ContactUs. You may also reach out to one of our Clinical Trial Nurse Navigators in our Clinical Trial Support Center by visiting LLS.org/Navigation.

Slide 47: LLS EDUCATION & SUPPORT RESOURCES

The Leukemia & Lymphoma Society offers financial assistance to help individuals with cancer. For more information, you can visit LLS.org/Finances. The Leukemia and Lymphoma Society is also a proud partner with Dollar For, a national nonprofit organization that helps patients apply for hospital debt forgiveness and eliminates medical bills. Their services are completely free. You can visit LLS.org/Dollarfor.

Slide 48: LLS EDUCATION & SUPPORT RESOURCES

You can download and print the slides as well as view today's program from our website, LLS.org/Programs under non-Hodgkin lymphoma. Again, we'd like to acknowledge and thank Eli Lilly Company and Kite, a Gilead company for their support of this program. Dr. Phillips, thanks again for volunteering your time with us today.

Slide 49: THANK YOU

On behalf of The Leukemia and Lymphoma Society, thank you all for joining us. Goodbye, and we wish you well.