TRANSITIONING FROM CHEMOTHERAPY TO MORE TARGETED APPROACHES IN MCL

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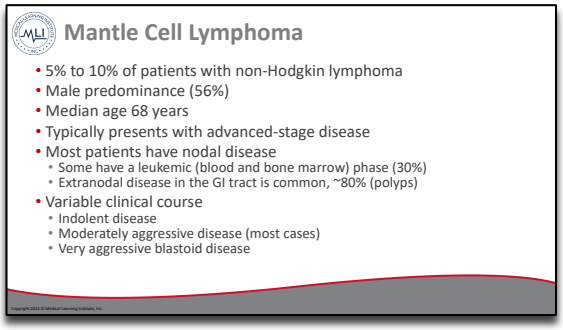
Dr. Flowers: Good afternoon, everyone, and welcome. Thank you for joining us for this symposium focusing on transitioning chemoimmunotherapy to more targeted approaches in mantle cell lymphoma.

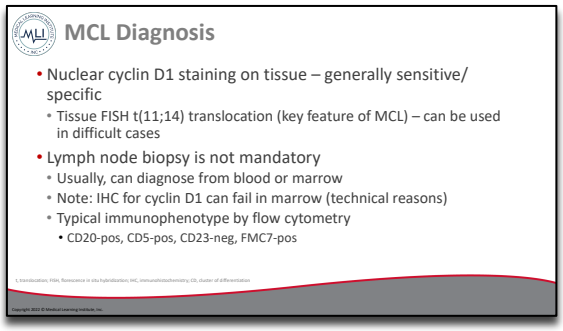
I'm Dr. Christopher Flowers. I'm Professor and Chair in the Department of Lymphoma/Myeloma and Interim Division Head for Cancer Medicine at the University of Texas, MD Anderson. And I'm joined by my colleague Jia Ruan, who's a Professor in Medicine in the Lymphoma Program at the Weill Cornell Medical Center.



Mantle Cell Lymphoma

Mantle cell lymphoma overall is a rare subtype of non-Hodgkin lymphomas. It represents about 5 to approximately 10% of patients who are seen across the United States with non-Hodgkin lymphoma, and the same is true in other Western countries.

It has a slight male predominance, and patients typically present in the late years of the sixth decade with an average age between the late 60s and early 70s. It typically presents with advanced stage disease with most patient having state III or stage IV disease at diagnosis with both nodal disease and sometimes extra nodal manifestations like leukemic presentation. And it's very common to find manifestations of the disease in the GI tract. In fact, if you do endoscopies to look for that, approximately 80% of patients will have mantle cell lymphoma found there if you do blind biopsies. And can have a variable clinical course with patients having a presentation that can be quite indolent and can involve approaches like observation alone to very aggressive. And you'll hear about some of those aggressive variant courses in the discussion that Dr. Ruan will go through.



MCL Diagnosis

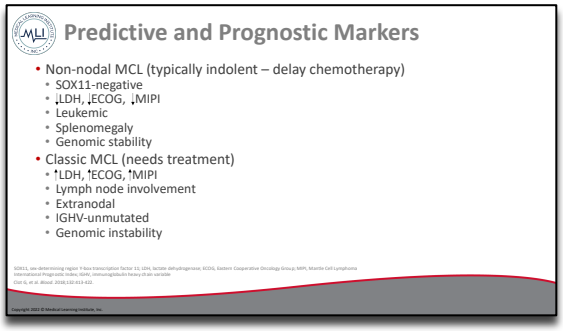
And so, when we think about the diagnosis of mantle cell lymphoma, these show some of the key diagnostic characteristics that are needed. The first is nuclear staining for cyclin D1 on a tissue specimen. Also, looking by FISH testing for the translocation 11:14 which is a key feature of mantle cell lymphoma that can help to distinguish it in difficult cases. And utilizing data or samples from bone marrow or blood that can be used for diagnostic criteria, even in some cases when lymph nodes are either not necessary or not available to be identified.

Shown at the bottom is the typical immunophenotype by flow cytometry, which could also be found sometimes on immunohistochemical stains where this is a CD5-positive, CD20-positive, CD23-negative, FMC7-positive lymphoma.

So, with that background, I will turn it over to Dr. Ruan who'll talk about some prognostic tools and ways to plan individualized therapy for patients with mantle cell lymphoma.

Dr. Ruan: Thank you, Chris. Hi everybody. I'm so happy to be here and thank you for the invitation for this discussion today.

I'd like to review the prognostic tools that we use in clinic to guide us to plan for individualized treatment for patients with a mantle cell lymphoma.

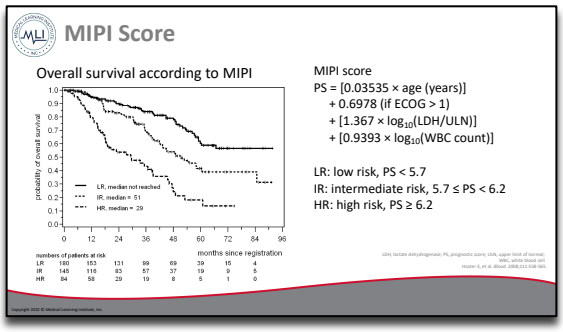


Predictive and Prognostic Markers

So, to start off, mantle cell lymphoma does have its heterogeneity. I think we learned that from gene expression array studies and more recently the Nano String expression panel. There's an entity called non-nodal mantle cell lymphoma which tends to be more indolent. I would say maybe about 30% of mantle cell lymphoma that we see in clinic.

And they're characterized by SOX11. Generally negative by IHC. They tend to have lowish LDH and a good ECOG status because patients tend to be not very symptomatic. MIPI score can be low. We'll come back to that. And like Dr. Flowers said patients could have leukemic presentations and they have splenomegaly but not very much nodal presentations. I would say that behind all of this perhaps is its biology in terms of relative genomic stability.

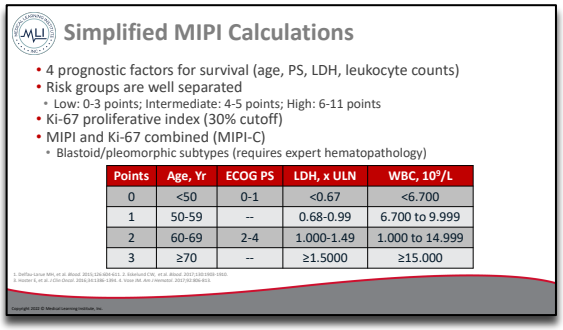
And that's to be contrasted with a classic form of mantle cell lymphoma, which we see for the majority in our clinic. They tend to be needing treatment more, relatively sooner compared with those with non-nodal mantle cell lymphoma. We could be impressed with their clinical presentation with elevated LDH. They tend to be symptomatic which affect their ECOG score and MIPI score can certainly be elevated as well. They could have extra nodal presentations, but I want to emphasize that lymph nodes tend to be more predominant for the classical mantle cell lymphoma. And one more thing, the IGVH status tend to be unmutated, which is probably behind its more accelerated growth pace. So molecular biology wise, mutations contribute to genomic instability that's behind nodal mantle cell lymphoma and account for its more accelerated pace and, therefore, the need for consideration of treatment.



MIPI Score

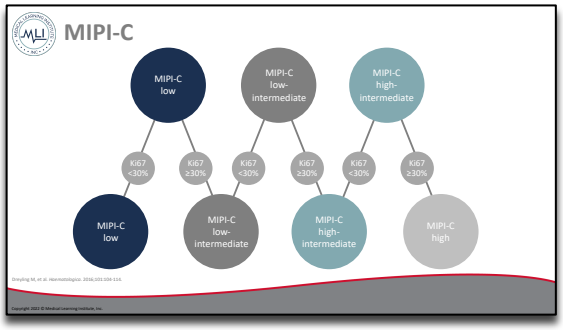
Very quickly, in terms of very classic prognostic score, the MIPI score, which is very familiar to you, utilizes four clinical parameters that are easily obtainable in our clinical practice. They include age, ECOG status, and LDH for chemistry value, and WBC count. And we know that there are three risk factor groups – the low risk, intermediate risk, and high risk.

I do want to comment on that because of age involvement in the MIPI score it's a continuous variable. Sometimes for elderly patients perhaps it is overly weighted on the MIPI. And likewise for younger patients even if you see someone with relatively low MIPI or intermediate risk MIPI, have to think about what's the biology behind it and is this underweighted in terms of their risk



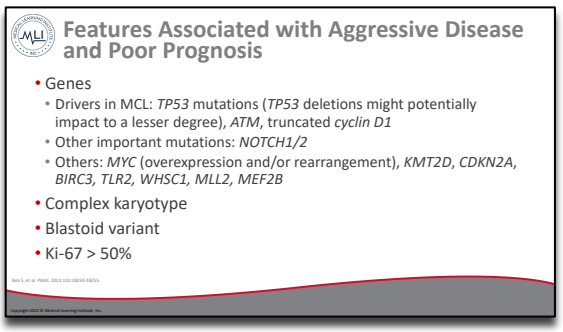
Simplified MIPI Calculations

To make it easier, there's a simplified MIPI score calculation and you have the points accordingly listed here. And to add more biological aspect to our risk prognostification, we sometimes use Ki-67, which is a clinical parameter for the growth signature that characterize mantle cell lymphoma. We can add Ki-67 to our MIPI in MIPI-B and, more recently, there's a MIPI-C score, which has a dichotomy of Ki-67 of 30% cutoff.



MIPI-C

And as shown here, what this MIPI-C score is really just to streamline the extreme spectrum for the MIPI particularly in the high MIPI category to differentiate between Ki-67 30% or below. For those over 30% for Ki-67, the MIPI-C really delineates a group of patients with high risk more concretely than the regular MIPI score. And likewise on the lower ending spectrum, it really filters out for patients with very low risk if you consider the Ki-67 percentage 30% as a cutoff. So just another way of looking at the prognostic score specifically for mantle cell lymphoma take into consideration the Ki-67 where it stands.



Features Associated with Aggressive Disease and Poor Prognosis

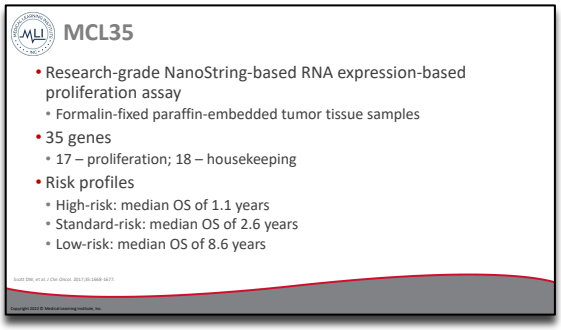
So, what are the parameters or biomarkers that we look at to help us understand is this an underlying aggressive disease and, therefore poor prognosis, and how do we intervene in terms of therapy?

So, there is a genetic aspect to that. There are driver genes in mantle cell lymphoma, most importantly the TP53 mutation. TP53 is very important, as you know, in many categories of

hematological malignancy. In mantle cell lymphoma in particular, mutations weigh more than mere deletion. There are other genes which are quite preponderant in mantle cell lymphoma, including ATM, NOTCH1/2, and others as listed, some of which have to do with pathways that are important such as NF-kappa B. But I want to say that, for our clinical operational standpoint, we really pay a lot of attention to TP53 aberrancies here.

The other thing that we look at is complex karyotype, so it really reflects the underlying genomic stability versus instability. So, when you have very complex karyotype, it signals that there's a lot of instability going on, that you really have to be watching things carefully.

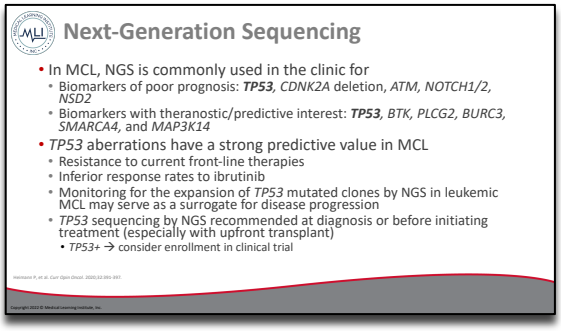
Blastoid variant is just the manifestation of instability with heightened growth rate and the cell looks very aggressive. And like we said before, Ki-67 with 30% we commonly use in clinic. And if you see somebody who's over 50, I think it's a warning sign that this is really a very high-risk condition that we're dealing with.



MCL35

We now do sequencing. It's next-generation sequencing. The ideal form is expression-based sequencing, the MCL35-gene panel, but it really is only available at selected research institutions.

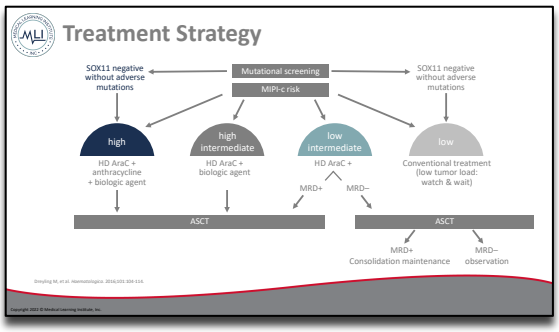
So, for our general practice, we actually resort to DNA-based next-generation sequencing. And the importance of that is that it can also differentiate the risk group based on the sequencing signature.



Next Generation Sequencing

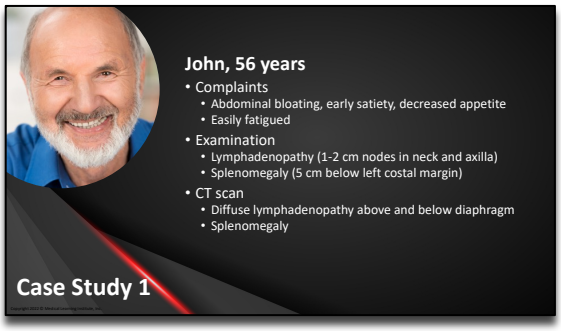
And as listed here, those sequencing panels easily can provide information on the TP53, aberrancy status, and CDKN2A, ATM, and other genes that are important for mantle cell lymphoma.

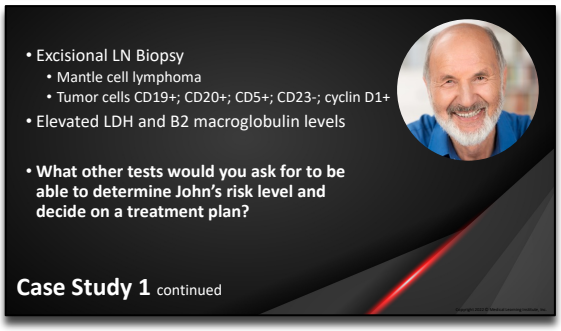
It's important to know the TP53 status because in those cases, we tend to observe resistance to current frontline therapy. Usually, it's chemoimmunotherapy based. And even for biological agents, they could respond, but the durability and the quality of response could be inferior compared with less high-risk cases. And we also would like to see the evolution of clones. and if there is some appearance of TP53 later on in the course of therapy, so on and, and so forth. So, we try to recommend screening for sequencing for TP53 and other type of genetic mutations.



Treatment Strategy

And as you can see here, we not only have the MIPI score, we have a modified MIPI-C risk which takes into consideration Ki-67. We also now have the availability of mutation screening. And for those patients with very low risk from both MIPI score, MIPI-C, and absence of those high-risk genomic mutations, we could certainly watch and wait for a little bit. However, for a patient with standard risk, without high-risk genomic mutations, we consider their age, performance status, and applicability of high-dose cytarabine in terms of their chemoimmunotherapy options and intensification with high-dose therapy and stem cell transplant for consolidation.





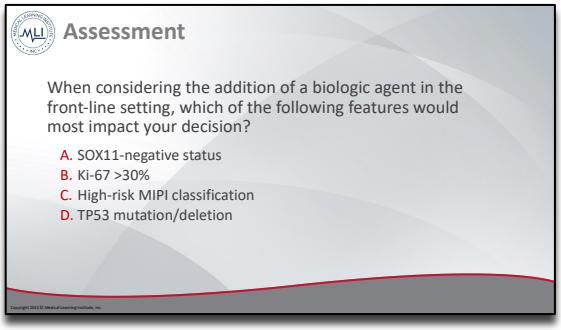
Case Study 1: John, 56 Years

So, we move onto a case. This is a patient 56-year-old. It's a fairly common age group that we see in our clinic, and he comes in with abdominal discomfort, bloating, early satiety, decreased appetite and is quite easily fatigued.

On examination there's palpable lymphadenopathies. Nothing bulky per se, but it's uncomfortable and noticeable. There's splenomegaly and CT scan confirms our suspicion that there's lymph nodes fairly diffusely involved above and beyond the diaphragm.

Lymph nodes biopsy was performed, and it came back with a fairly typical immunophenotypic panels at CD19, CD20, CD5-positive, cyclin D1 positive by IHC. There's elevated LDH, all of which contribute to our clinical impression and MIPI score as well.

So, what other tests would you would like to see before determining the risk levels and advise on a treatment plan?



Assessment

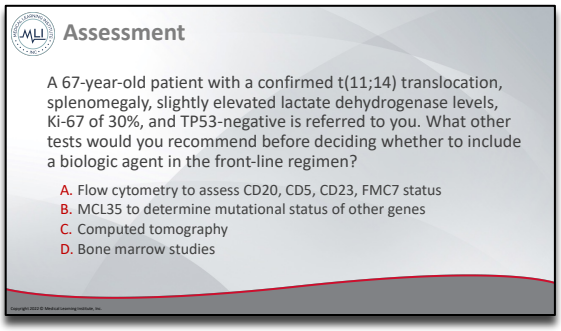
Dr. Flowers: Jia, how do you think through the challenges that a patient like that presents in terms of the strategies that you think about for
the workup?

Dr. Ruan: I think it's fairly typical. It's a male patient, less than 60 and physically fit, so our standard options would be chemoimmunotherapy. Before we consider further, we'd like to make sure that he doesn't have exceedingly high risk, such as TP53 mutations.

It is not to say that those patients are not chemoimmunotherapy candidates but really try to figure out are there better options, such as novel agents that are specifically designed for those risk group where they maybe have more efficacy and less side effects. Because of that, we want to look more in-depth at their genomic composition.

And as you can see here we have options here. What are the consideration when you want to consider addition of the biological agent in the frontline settings? We have SOX11 status, we have the Ki-67 evaluations, MIPI score as very classic sign, and TP53 mutations and deletion as options.

Wonderful. I'm very pleased with the response. We are looking for TP53 mutation.



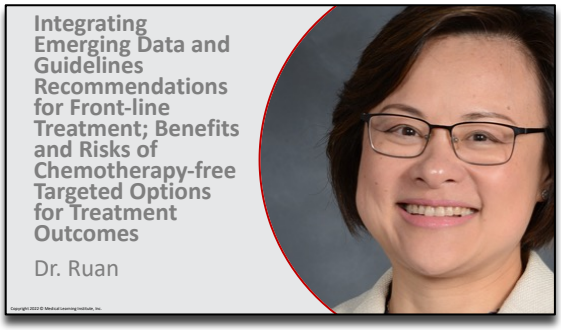
Assessment

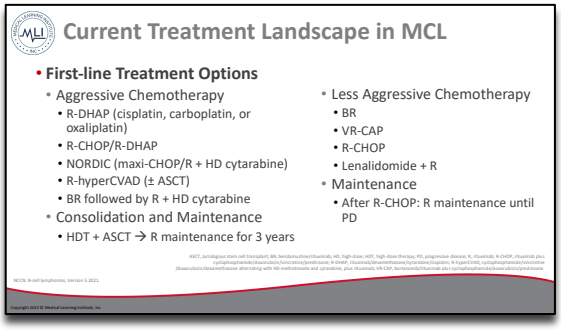
Dr. Ruan: So now we have a 67-year-old patient. It's a median age for mantle cell lymphoma. Very, very common to be seen in our clinic and has a translocation typical for mantle cell lymphoma, splenomegaly, and elevated Ki-67 30% and TP53 negative status.

What other test would you recommend before deciding whether to include biological agents in the frontline regimen? Well may I comment that perhaps here TP53 negative was based on the IHC. It's commonly performed in the majority of the pathology laboratories.
So here are the options, including flow cytometry, the ML35 panel that we kind of reviewed earlier which is into sequencing step, and CT scan bone marrow biopsy. But what would you like to know?

I agree and by now the flow cytometry was performed. We agree that sequencing will be very important. I just want to mention that for practical purposes, next-generation DNA sequencing might be the most practical. MCL35 would be ideal if there is a facility to do so.

The burning question is how to optimize treatment. The first-line therapy is really important and there's a lot of consideration, there's a lot of anxiety; and you're talking about not only understanding of the disease but also patients' preferences. And everybody wants a good outcome, but they also want less of the side effects. And I think we're into era in which there are lots of good options and the question is how to apply them. And waiting for data to come out of a lot of important studies.





Current Treatment Landscape in MCL

Dr. Ruan: So, we move on to discuss current treatment landscape in mantle cell lymphoma for first-line therapy. This should be very familiar to you. It is anchored on chemoimmunotherapy. It started with the intensity of treatment and, therefore, age and physical fitness play important roles historically because we like to offer high intensity treatment for those candidates. And they are rituximab combination with high-dose cytarabine-based backbone, and this could be followed with autologous stem cell transplant as consolidation. And we know that rituximab maintenance adds to your survival outcome.

For the majority of the patients who are not candidate for aggressive therapy, then less aggressive chemoimmunotherapy backbone become very, very important. And I think that's widely used in our clinical practice. It is represented by bendamustine-rituximab combination, the VR-CAP, which is a variant of CHOP but replacing the vincristine with bortezomib, and then R-CHOP. It really refers to R-CHOP with a maintenance with rituximab. And then you could also use a nonchemotherapy-based combination of lenalidomide plus rituximab.

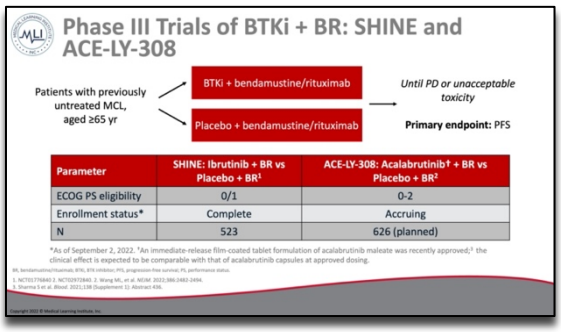
And maintenance is supported by evidence for after R-CHOP and also after autologous stem cell transplant. So how can we approve based on those foundations?

Dr. Flowers: There are a lot of choices there on that slide, right. Maybe for those who don't see as many mantle cell patients as you do on an everyday basis, how do you select from those options in your practice and which ones do you use most commonly?

Dr. Ruan: That's a good question, and I have to say that conversation is always very individualized and very different no matter how many times you talk about similar scenarios because the majority of the patients are in the border age group where they could be a candidate for very intensive therapy, but they could also be using a modest intensity backbone such as bendamustine.

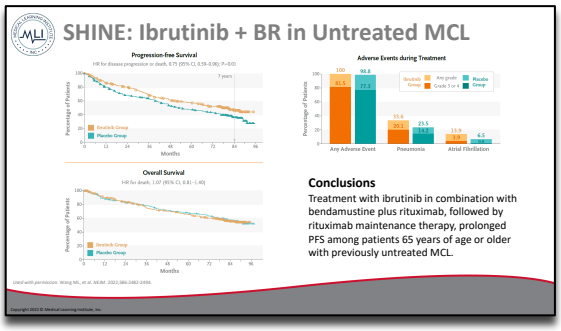
I must say that the data coming out of Alliance and others to show that BR can really go to a high-quality response measured by MRD. So, it is a formidable choice, and I think it's a great one because it caters to pretty much everybody seen in our practice. We also have the advantage of having a very active clinical research group, so we always have some clinical trials available with a lot of choices of novel agents, so that's what we talk about. But they are patient wanting to have a very finite duration treatment and then be done with it and not bothering with chronic therapy or maintenance. And to that, I say that, you know, high intensity chemoimmunotherapy continues to have its place. But, again, it's not easy.

I want to also add that the discussion evolves also with patient, especially for those with a lot of watch-and-wait options and their perspective and preference changes. And so that's a good thing. And we, we do have options to offer to all of them.



Phase III Trials of BTKi + BR: SHINE and ACE-LY-308

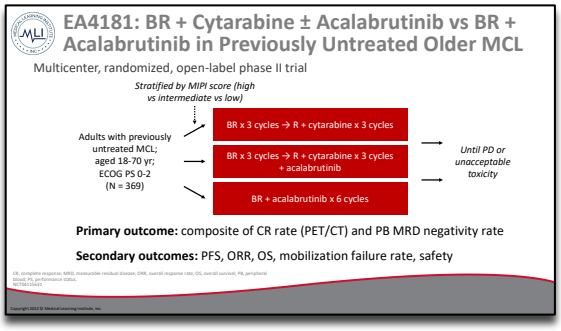
So, moving on to addition of novel agents to the chemoimmunotherapy backbone. So, as you can see on this slide, really it kind of lines up in terms of our knowledge and available data. So, the earliest one that with a readout is the SHINE study which just came out this year. SHINE study and in parallel the acalabrutinib combination, the ECHO study, they're very similarly designed, essentially looking at bendamustine-rituximab as a backbone and comparing that to adding additional BTK inhibitor, either ibrutinib in the SHINE design or acalabrutinib in the ECHO study. And those patients were otherwise treated very standardly with BR, some with rituximab maintenance for a brief period, and then continue on with either ibrutinib or acalabrutinib versus placebo. So, the question is: is this feasible and can we observe a synergistic improvement in terms of outcome?



SHINE: Ibrutinib + BR in Untreated MCL

This is the SHINE data which was reported after seven years of follow up which is remarkable. There's no difference in terms of overall survival because the two curves essentially merge to each other, but the left upper panel shows the progression-free survival separated very early on and persisted over seven years and hopefully beyond that. The triplet, ibrutinib plus BR, is more favorable. Has improved progression-free survival compared with BR. And so, we're talking about median progression-free survival in the BR arm of four years, expected to be about seven years in the ibrutinib-BR arm.

And toxicity panel on the right, overall, they're very comparable for the BTK inhibitor-specific AE category like atrial fibrillations and others, maybe there's some increased toxicity. And it's important to review both efficacy and side effects because the ongoing treatment certainly would continue to be exposed to those side effects, so they potentially could be accumulative. It's always important to know, and then how that's going to be evolving with ongoing follow up. So, it's very, very important data because that's really the first one that we have that adding the novel therapy to immunochemotherapy backbone.

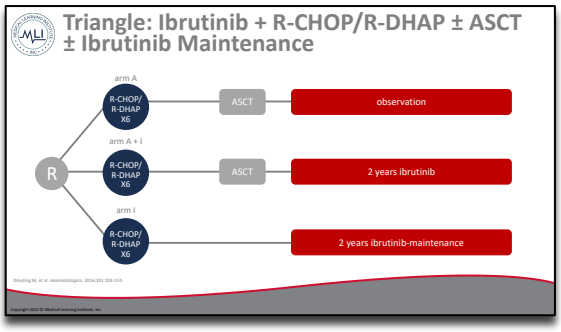


EA4181: BR + Cytarabine ± Acalabrutinib vs BR + Acalabrutinib in Previously Untreated Older MCL

Subsequent slides really just a preview of study results to come and there's lot of them, and I think it's very, very exciting. So, one of them is the ECOG EA4181 study where it's not only BR plus the BTK inhibitor, but this time to introduce onto the backbone of cytarabine, because cytarabine was very active in mantle cell lymphoma and it can be combined with BR. So, can this be added further with a BTK inhibitor?

And, and this study will attempt to address all of that with a three-arm design. As you can see here, the lower arm is actually the comparator. And then the top arm is looking at bendamustine-rituximab and adding the cytarabine. And the middle arm is the experimental arm where the acalabrutinib will be added

as well. So, it would be very interesting to see how well that's tolerated and do they really add some leverage for high-risk conditions.

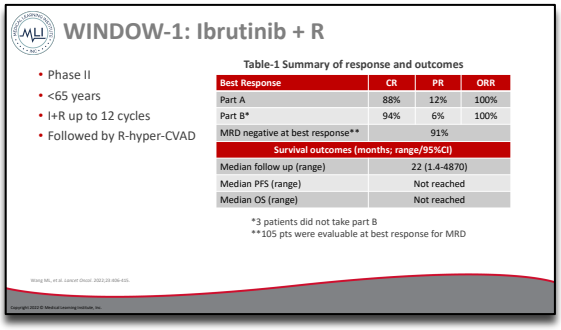


Triangle: Ibrutinib + R-CHOP/R-DHAP± ASCT± Ibrutinib Maintenance

And the other more intensive study was the Triangle study. It's a European-based study, and it's maturing.It really is adding to the European Mantle Cell Lymphoma Network. The R-CHOP and RD have alternating strategy and followed by stem cell transplant. And in this study, they're adding ibrutinib to that backbone. And then the second arm is to ask could ibrutinib do just as well without autologous stem cell transplant? I believe those are all very, very important questions to ask and especially in the high intensive chemoimmunotherapy backbone type of approach. So, we look forward to those outcomes.

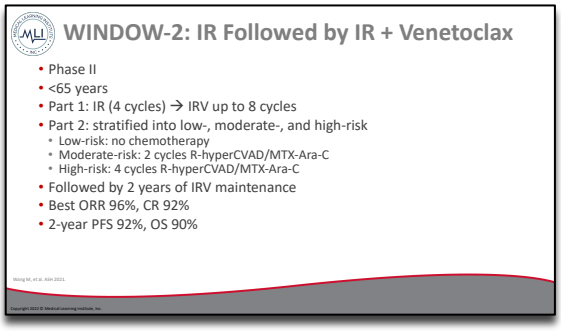
Dr. Flowers: Hoping to see some results from that at this year's ASH meeting.

Dr. Ruan: Yeah, that would be very good. That will be really exciting.



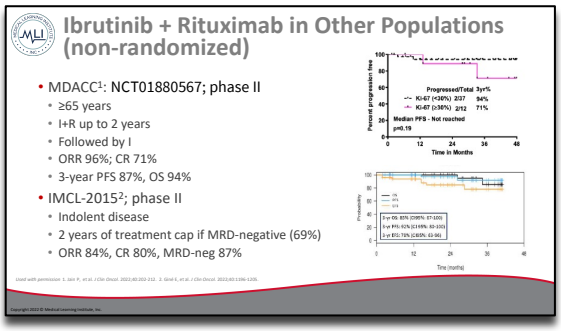
WINDOW-1: Ibrutinib + R

The other question to ask is: can a novel therapy be used for induction and then followed by high intensity such as hyper-CVAD? So, we're talking about this, a wide spectrum of approaches but really concentrated into one study. And those are the WINDOW studies. The WINDOW-1 was published, and it is ibrutinib plus rituximab as induction up to 12 cycles and then followed by R-hyper-CVAD. It's conducted here at MD Anderson by Dr. Wang's group. And as you can see here, the efficacy is flying off the wall. It's 100% overall response rate, 94% CR, and it would be good to see how in the long term this approach is evolving and very valuable evidence for adding novel therapy to chemotherapy backbone.



WINDOW-2: IR Followed by IR

And WINDOW-2 is ongoing, I believe. And this is a triplet induction. This is not only ibrutinib-rituximab but venetoclax and adding risk-stratified chemotherapy consolidation. So, you know, we're very excited to wait for those results.

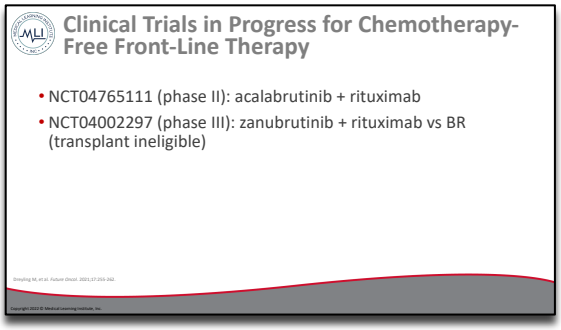


Ibrutinib + Rituximab in Other Populations (non-randomized)

So not only can the novel agents complement chemotherapy, can they do away with it, especially in some selected populations at least for the data that we have?

So ibrutinib plus rituximab in elderly nonchemotherapy or not preferred population this is a study by MD Anderson and a study from Europe, the Spanish group. And they have 50 patients each and they receive treatment up to two years. And I think one of them actually can stop the treatment.

And as you can see here, on the efficacy curve, it looks just very, very good. And it is chronic therapy. At three years, like 80%, 85% of patients are still in remission and some of them may already have stopped treatment. So that is quite exciting and refreshing, and really requires more follow up, larger study, and maybe a comparison to really know where that really fits in terms of for majority of our patients.

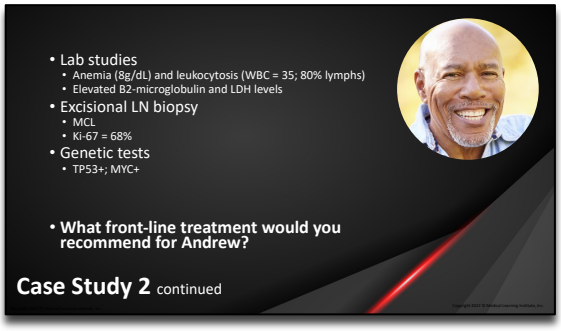


Clinical Trials in Progress for Chemotherapy-Free Front-Line Therapy

This is a list of trials of others that are ongoing as we alluded before that it will be nice to compare that directly with those also employing chemoimmunotherapy to see if this merit to one or both of the arms and how to select.

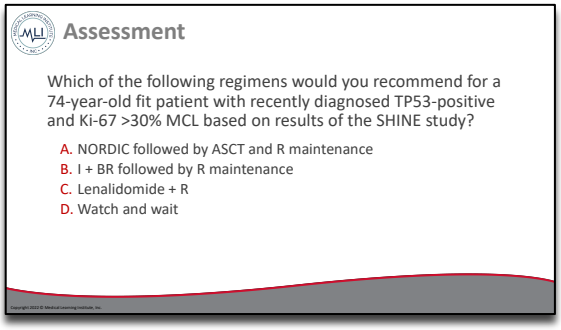
Case Study 2: Andrew, 75 years

So, we're going to jump right into another case in the frontline therapy choice category. This is patient Andrew, 75-year-old, which is also very typical to be seen in our clinic for mantle cell lymphoma. And this one also comes with a lot of comorbidities to be expected for that age group with hypertension medication, cardiac insufficiency and seems to be symptomatic with fatigue, weight loss and decreased appetite. There's a lot of disease with splenomegaly and lymphadenopathy.



So, this was further supported by the lab studies, and they have cytopenias, leukocytosis, a lot of them in the blood, and elevated LDH. And a lymph node biopsy was very important because the Ki-67 was very high, over 50%. You can't wait. The genetic testing also come back: TP53 positive with c-Myc, which tend to go along with very high-growth index.

What type of frontline treatment would you recommend for this patient?



Assessment

So, your options include high intensity NORDIC regimen, autologous stem cell transplant and rituximab maintenance. You could have bendamustine-based plus ibrutinib like what we do for SHINE and the rituximab maintenance, lenalidomide plus rituximab, and then watch/wait.

So, yes, we would easily exclude (A) because of age group and comorbidity. Watch and wait most likely not. Lenalidomide-rituximab certainly fair for elderly population, but for the high risk there's no data to support its long-term outcome. So, I agree that BR plus ibrutinib followed by rituximab maintenance is a very fair option to try.

Oh, there's a question.

Speaker: Hi, wouldn't we be worried about side effects with ibrutinib with his cardiac and other comorbidities?

Dr. Ruan: Yes, we thought about it.

Dr. Flowers: I think this is a patient population that is very complicated, and this case was purposely written to be quite complicated. In clinical practice the catch here is it's based on the SHINE study and so based on the that study; the preferred regimen really would've been ibrutinib-bendamustine-rituximab based on the data that Dr. Ruan just presented. I think in clinical practice, as she alluded to, this might be a patient that you would think about lenalidomide-rituximab given your experience perhaps, although the, the TP53 might give you some pause.

Dr. Ruan: Yes, it does. And then you wonder that the next generation BTK inhibitor might be more appropriate. Again, sometimes is constrained in terms of our practice and there's also constraint in framing the question and the answer. So, whether acalabrutinib or zanubrutinib combination would offer a better toxicity profile, it's waiting to be seen. Yeah, but great question. I would be concerned as well.

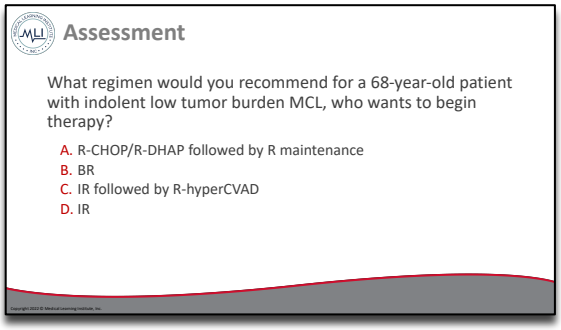
Dr. Flowers: Yeah. This is a patient description where there are a lot of tough options among these choices, among the ones that were available there. And I think this is probably the best of, of those options. I think in particular the NORDIC regimen and stem cell transplant in the patient population that's TP53 positive is something that you shouldn't put a patient through that level of toxicity for the expected limited benefit that you see there.

Dr. Ruan: And in the older days where we don't have next-generation BTK inhibitors, sometimes you just have to try it. You know, bite the bullet and, and treating any other side effects as appropriate. So, it's sort of doable in that sense.

Dr. Flowers: Looks like there's another question out there.

Speaker: You said, Dr. Flowers, that among the options there that you think that that's the best choice, but if you were unrestricted in your choice for upfront treatment of TP53 and mantle cell lymphoma, I'm intrigued as to what your choice would be and whether you'd consolidate with either form of transplant.

Dr. Flowers: These are the kinds of patients that we would very commonly put on a clinical trial that used a chemotherapy-free approach. And so, approaches like what you heard from Dr. Ruan using one of the WINDOW approach studies. We're now currently enrolling patients on WINDOW-3. This is the kind of patient who's at an age group and a comorbidity level that may or may not be appropriate for that study but might be on the borderline. And in those patients, we're thinking about intensive induction regimens with a BTK-based upfront approach followed by consolidation with CAR T cells. And so, I think those are the kinds of approaches that we might think about on a clinical trial for a patient like this.
The other kinds of approaches that we have inside of the clinical trial are like the approach that you just heard from Dr. Ruan using ibrutinib, venetoclax, and rituximab but with follow-up trials to that one.

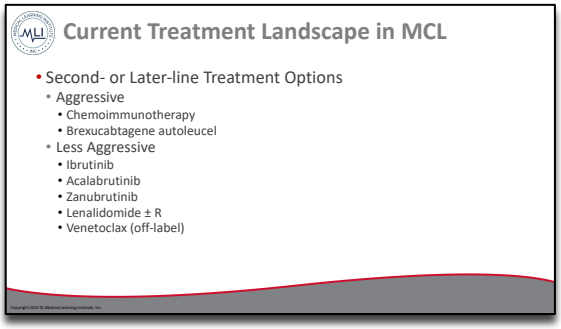


Assessment

Dr. Ruan: Let's move onto the next one. And so here you have a 68-year-old patient with more indolent picture and low tumor burden, but who wants to start therapy? We do see those patients. So here you have options.
So, the R-CHOP/R-DHAP alternating followed by R maintenance, bendamustine-rituximab, and ibrutinib-rituximab followed by R-hyper-CVAD, which is WINDOW-1 format, or the ibrutinib and rituximab combination, which is free of conventional chemotherapy. What do you think?

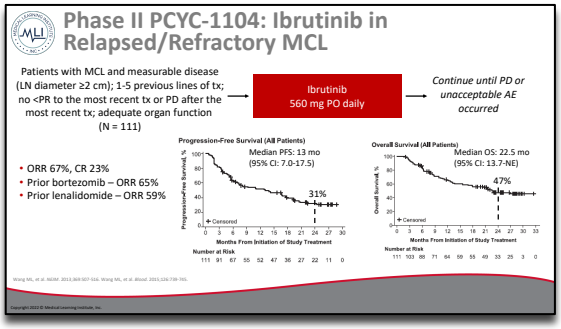
This is a scenario where there's a lot of discussion going on in clinic because they could be watch and waited. They could certainly start treatment and there's many good options and you don't want to have too intensive therapy with bad side effects for long-term sort of response longevity. So, the response is the chemotherapy-free ibrutinib rituximab because I think people are impressed with the report on those two studies. And then the opportunity or feasibility even to contemplate stopping the ibrutinib.
And then the bendamustine-rituximab is very well tolerated, and most people are very familiar in terms of dosing and taking care of the side effects. So, I think that was good.

Dr. Flowers: Thanks, Dr. Ruan. I will talk you through the next section about the novel therapies and approved therapies in the second- and third line setting for relapsed and refractory mantle cell lymphoma.



Current Treatment Landscape in MCL

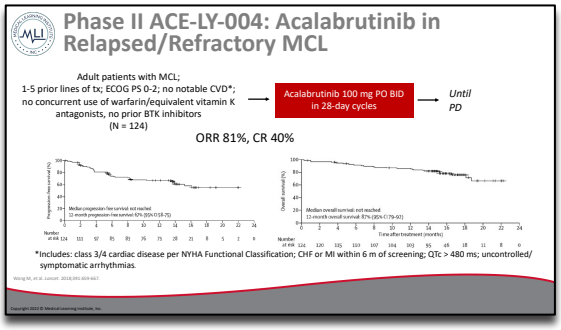
And so, as we think about the current landscape, these are many of the options that I will talk through. Approaches like chemoimmunotherapy that still exist in the relapsed setting, although it is much, much less commonly used, the approach of chimeric antigen receptor T-cells with brexucabtagene autoleucel for mantle cell lymphoma, and other approaches like the BTK inhibitors listed there – lenalidomide, rituximab, or the use of venetoclax as a single agent.



Phase II PCYC-1104: Ibrutinib in Relapsed/Refractory MCL

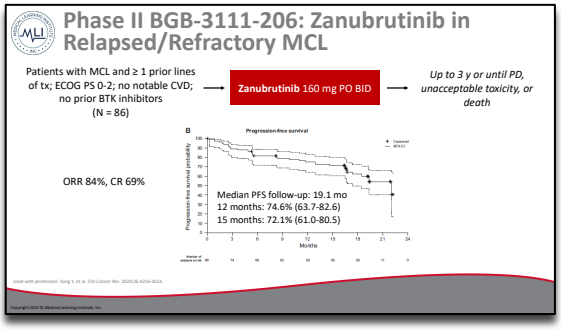
As we think through these data, you heard about a number of studies that were presented in the frontline by Dr. Ruan that were led by my good friend and colleague, Dr. Michael Wang, the SHINE study as well, and the WINDOW-1 and WINDOW-2 studies. I will make sure that as I talk about his data in the relapsed setting that I'm very precise. I'm worried that Michael will run in the back of the room at any point in time from his office across the street and say, "Wait, you're not presenting my data correctly."

He's really been a key leader in the development of novel therapies for mantle cell lymphoma. And here with the first of the Bruton's tyrosine kinase inhibitors in mantle cell lymphoma with ibrutinib, which is given as you see there at 560 milligrams per day. And you can see that this has had a fairly favorable overall response rate and complete response rate as the first of these BTK inhibitors approved and then with a median progression-free survival of 13 months in this pivotal study.



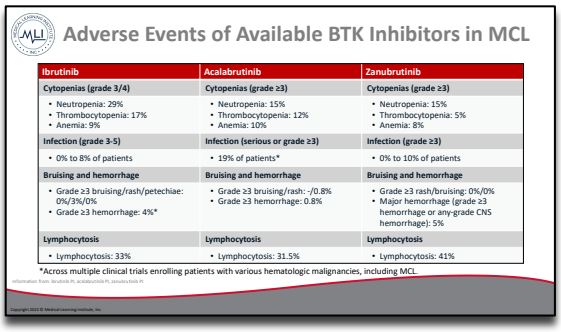
Phase II ACE-LY-004: Acalabrutinib in Relapsed/Refractory MCL

Additional data have led to the approval of acalabrutinib with studies that were also led by Dr. Wang where that's given at 100 milligrams twice daily. And we'll talk in a little bit more detail about the various BTK inhibitors and how they compare in terms of their adverse event profile. You can see here that the overall response rate was 81% with a CR rate of 40%. Higher than what I describe in the prior trial, but, again, these patient populations are slightly different in terms of the patients that were enrolled in the trial. And it's not really fair to perform head-to-head comparisons in terms of the efficacy of these agents. But, again, this led to approval of a new agent with this single-arm trial.



Phase II BGB-311-206: Zanubrutinib in Relapsed/Refractory MCL

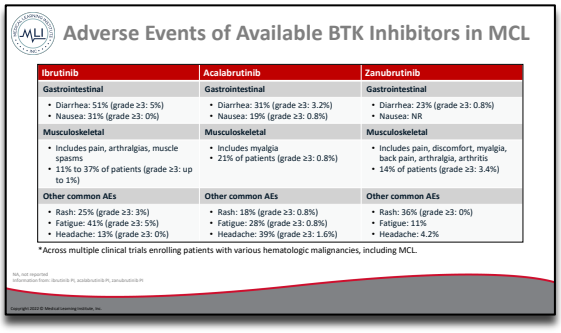
And then here are shown the data from zanubrutinib that is also approved here at a dose of 160 milligrams given twice daily. You can see an overall response rate of 84%. And, again, a fairly favorable and relatively similar progression-free survival curves with a median progression-free survival of 19 months in this patient population.



Adverse Events of Available BTK Inhibitors in MCL

And so, when we think about the Bruton's tyrosine kinase inhibitors, I think it's important to think about them in terms of their adverse event profiles. Some of the adverse event profile across all the agents within this class are quite similar, but there are some areas like bruising and hemorrhage where the second and later generation Bruton's tyrosine kinase inhibitors have a lower risk of events like bruising and in particular serious bleeding.

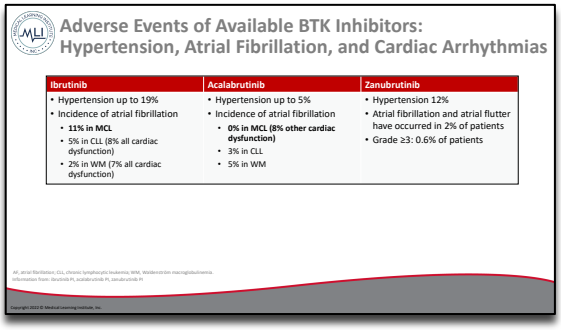
Some of that has come over time as we've learned with experience how to use these agents and which patient populations not to use them in and particularly avoiding concomitant use of agents like warfarin with these agents. But some of them are actually other events that we see that maybe are less common or in the newer agents like acalabrutinib and zanubrutinib.



Adverse Events of Available BTK Inhibitors in MCL

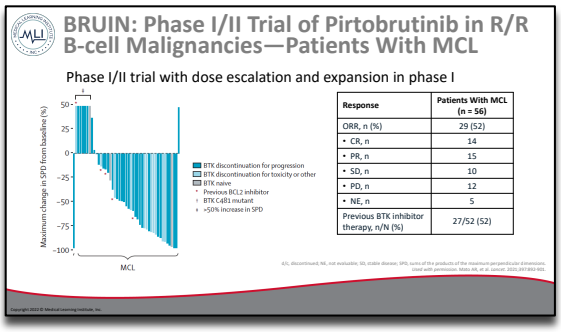
This shows in terms of the gastrointestinal adverse events which also are quite common and perhaps also a little bit less in the newer agents where you can see rates of diarrhea overall are reasonably common, but those rates of grade 3 or greater diarrhea are actually quite low across the agents, particularly for the newer agents. And you can see that other common events are rash that occur anywhere between about 20% to about a third of patients who have this as an adverse event. But that tends to be mild and self-limited, and time limited in duration.

I think perhaps one of the things that is a newer adverse event that we've seen more commonly, particularly with acalabrutinib, is the role of headache which patients will experience and that also can be ameliorated with caffeine.



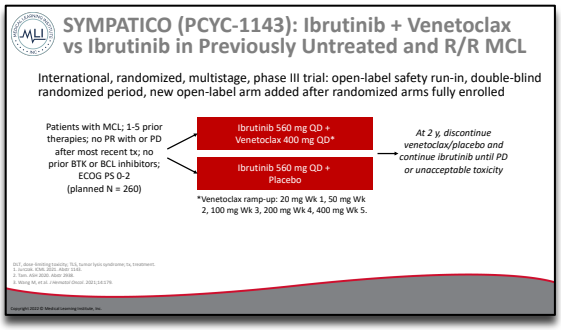
Adverse Events of Available BTK Inhibitors: Hypertension, Atrial Fibrillation, and Cardiac Arrhythmias

And then finally turning to the cardiovascular adverse events that were alluded to during the earlier discussion about one of our patients in the cases, that's something that has been seen to be lesser in the newer agents. Particularly the risk of atrial fibrillation with zanubrutinib/acalabrutinib appears to be markedly less in those patient populations.



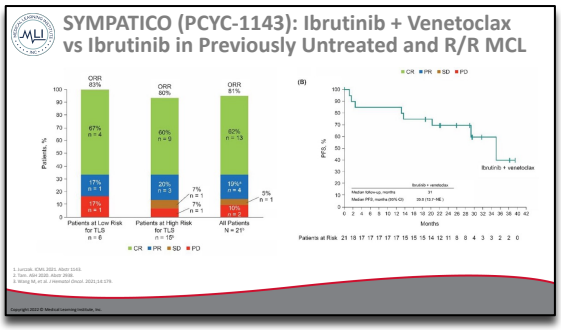
BRUIN: Phase I/II Trial of Pirtobrutinib in R/R B-cell Malignancies – Patients with MCL

So, turning attention now to other novel agents in the class in the covalently bonded Bruton's tyrosine kinase inhibitor pirtobrutinib is now moving forward in clinical trials. And here you see quite high overall response rates in a relapsed and refractory patient population. And the waterfall plot is shown to the left with the CR rates in 14 of the 56 patients who were treated in this Phase I study.



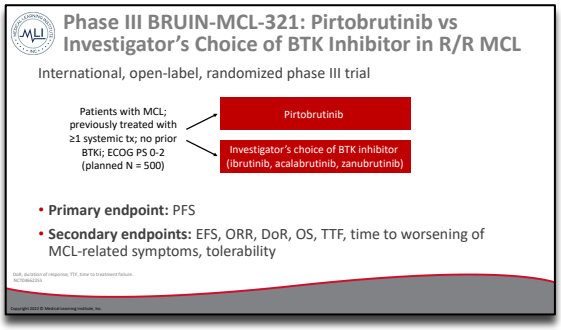
SYMPATICO (PCYC-1143): Ibrutinib + Venetoclax vs Ibrutinub in Previously Untreated and R/R MCL

We now are looking in the relapsed and refractory setting at other combination therapies. This is the structure of the SYMPATICO trial that was a combination of ibrutinib-venetoclax in a randomized fashion versus single-agent ibrutinib in relapsed and refractory mantle cell lymphoma as well as some patients who had untreated mantle cell lymphoma who enrolled on this trial.



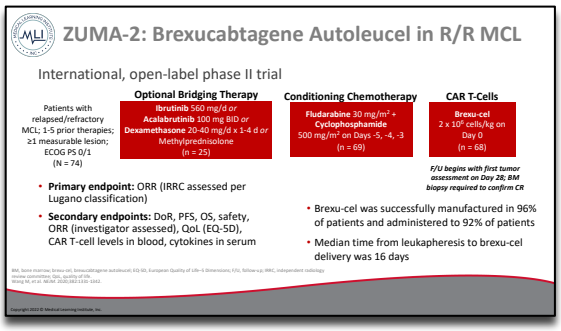
SYMPATICO (PCYC-1143): Ibrutinib + Venetoclax vs Ibrutinub in Previously Untreated and R/R MCL

Here are the arms for the ibrutinib-venetoclax group and the overall response rate was quite high, both in the low risk for tumor lysis syndrome patient population and the high-risk patient population, with an overall response rate of 81% in the trial and a progression-free survival curve for the ibrutinib-venetoclax arm that also looks quite favorable in this setting.



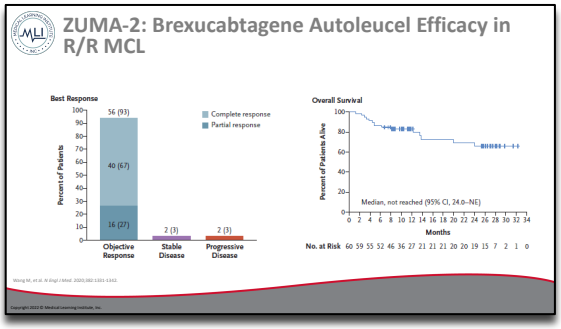
Phase III BRUIN-MCL-321: Pirtobrutinib vs Investigator's Choice of BTK Inhibitor in R/R MCL

The next trial that I'll turn to is the next BRUIN trial which is looking at pirtobrutinib in a randomized fashion using that versus the investigator's choice of BTK inhibitor in the relapsed and refractory setting with the primary endpoint being progression-free survival. And I think this will help to speak to where this agent really lies in direct head-to-head comparison to the other BTK inhibitors. And so, we're looking forward to seeing data from that trial in the future.



ZUMA-2: Brexucabtagene Autoleucel in R/R MCL

The other agent that I alluded to that fell into the aggressive component of the slide at the, the top was the use of brexucabtagene autoleucel, the CAR T-cell therapy. So, a CD19-targeted CAR T-cell therapy for patients with mantle cell lymphoma where patients could have received bridging therapy with either ibrutinib or acalabrutinib or steroids prior to going on to lymphodepleting conditioning therapy and then went on to receive CAR T-cells with brexu-cel.



ZUMA-2: Brexucabtagene Autoleucel Efficacy in R/R MCL

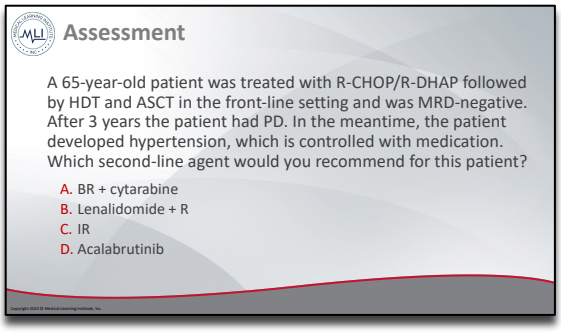
This had a very high overall response rate for patients with relapsed and refractory mantle cell lymphoma, with a 93% overall response rate and a fairly favorable progression-free survival curve. These survival curves are not quite as long out as that we've seen for diffuse large B-cell lymphoma, but I think look quite promising for the early phase of these survival curves.

Case Study 3: Nicole, 58 years

So, let's turn to a few cases to describe patients that we see in the relapsed and refractory setting. This is a 58-year-old woman. As I mentioned from the outset, it's much more common for men to be diagnosis with mantle cell lymphoma, but we do see women with mantle cell lymphoma who present both in the frontline setting and in the relapsed setting. In the frontline setting, this younger woman had aggressive treatment with the NORDIC regimen and then was being seen for regular follow-up appointments. And in her regular follow appointments had recurrence detected by scans.

And at this point after having an aggressive regimen in the frontline, she indicated that she wanted to have a less aggressive regimen. And I think among those second-line therapies, there were a number of regimens

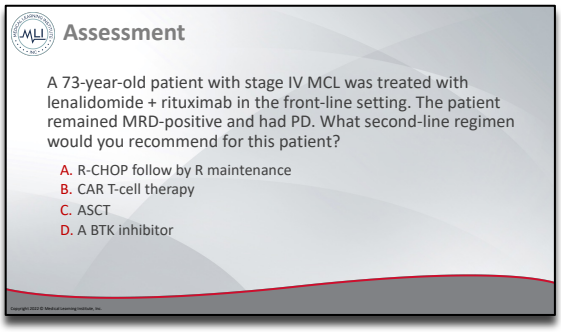
that I alluded to that would be possibilities, including all the BTK inhibitors and lenalidomide, which is used much less commonly in this setting but still available as an approved agent in this space.



Assessment

So, let's turn to a question for a similar type of patient. So, this is a 65-year-old patient who was treated with an aggressive regimen in the frontline setting, the R-CHOP/R-DHAP alternating regimen, and then went on to have high-dose therapy and autologous stem cell transplant. He was noted at the completion of treatment to have no evidence of minimal residual disease so was MRD negative, but three years after his transplant was noted to have progression of disease. And in the meantime, the patient has developed hypertension which has been a little difficult to control. And so, which of these second-line regimens would you consider for this particular patient?

So, it looks like 100% of you chose acalabrutinib. I think that among these choices really is the choice that I also would choose. Given the hypertension that was difficult to control, this would be a patient who would be a better candidate for a second-generation BTK inhibitor that's likely to be better tolerated. And that's indicated as the correct choice. So, looks like folks were listening and all of you got that one right.

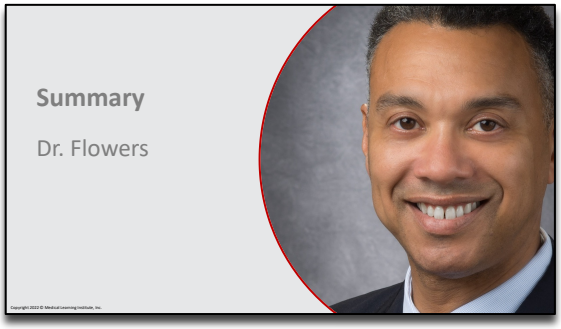


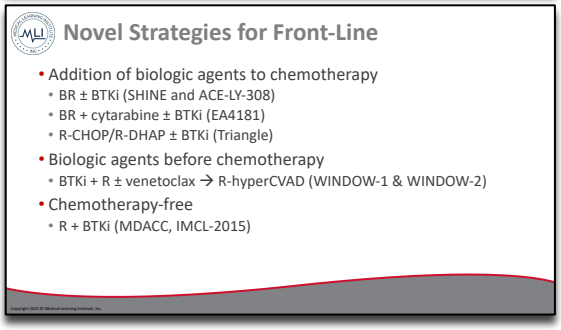
Assessment

So, the next patient is a 73-year-old patient with stage IV mantle cell lymphoma who was treated initially with lenalidomide and rituximab in the frontline setting. The patient remained MRD positive and then ultimately had evidence of progressive disease. What second-line regimen would you recommend for this patient? R-CHOP followed by R maintenance in the second line, CAR T-cell therapy, stem cell transplantation, or a BTK inhibitor.

Looks like, again, all of you got that one right. Either my questions are too easy or all of you are actually learning quite a bit in this session. And so, the correct answer is BTK inhibitor.

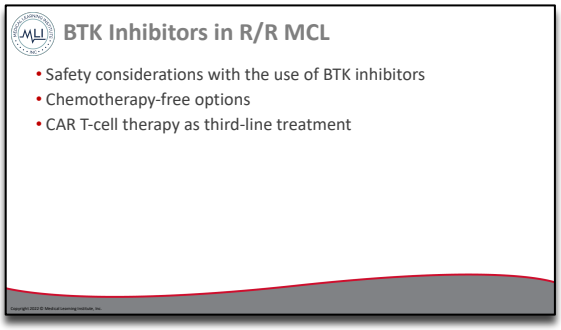
You know, there are a couple of these other options that I think are ones that you might consider. It's a little bit early for CAR T-cell therapy in this patient who only had one frontline regimen. R-CHOP followed by R maintenance would've been a common approach in years past, but I think now R-CHOP is more commonly used in the frontline setting or not at all for patients with mantle cell lymphoma. And stem cell transplant we can typically consider in the frontline setting as a component of the frontline aggressive care and, and not as a relapsed regimen for mantle cell the way we have in the past for other lymphoma subtypes. And as I mentioned, we'll see more data about how that should be used at the ASH meeting.





Novel Strategies for Front-Line

So just to summarize, we reviewed novel strategies in the frontline and you heard about data from the combination of bendamustine-rituximab and BTK inhibitors in two studies, the data that we're hoping to see in upcoming meetings using bendamustine-rituximab and cytarabine plus a BTK inhibitor as well as the Triangle study that's looking at autologous stem cell transplantation versus BTK inhibitor as a maintenance following R-CHOP/R-DHAP for aggressive-behaving lymphomas in the frontline setting, as well as biological agents in the frontline and some chemotherapy-free approaches in the frontline as well.



BTK Inhibitors in R/R MCL

And in the relapsed setting, we've talked about the safety considerations for the BTK inhibitors as well as some of these chemotherapy-free options as, and CAR T-cell therapy.

Q&A

So, with that, we'll open it up for any questions if there are questions from the audience or any questions coming in online. So please raise your hand if there are questions.

Speaker: Thanks. the last two cases you mentioned MRD. I'm just interested in how you're measuring MRD and how you use MRD to inform your practice.

Dr. Flowers: We had a little bit of this discussion ahead of the meeting. I'll let you start, Dr. Ruan, and then I'll make some comments.

Dr. Ruan: I think it's a great question. You know, for now, I think it's a very attractive biomarker and a majority of the studies, the major studies, either Phase II or Phase III, we do have MRD data. I think I use those data to assess the quality of those treatment regimen. You know, if the MRD rate is very high, I rate

those treatments as being very effective. And they tend to correlate with a better progression-free survival. I think we do have data on that.
As to how much are we using MRD in terms of formulating or adjusting for our individual patients, in our practice, the MRD is limited to clinical trials, so we collect MRD, and we follow what needs to be carried out for the trial design. But I think it will eventually become more adopted in terms of adjusting for treatment.

Especially with novel agents, we're doing this as maintenance for a year or two or three, so the question would be could MRD become a guidance in terms of duration of maintenance?
Another scenario would be if somebody who was in MRD negative remission become MRD positive, how closely should we follow them and should we reintroduce their maintenance based on MRD status? So, I think there are more questions for MRD than answers, but, but I think it's a very, very important biomarker that we should try to accumulate data on.

Dr. Flowers: And I agree with everything that you've said. I think the short answer to your question in terms of how are we using MRD clinically is: not as well as we should be. I think there have been some challenges. One has been that MRD collection within the context of clinical trials has not been consistent. We haven't used similar consistent methodology across trials. We haven't used similar consistent timepoints for MRD assessment and evaluation. And so, it makes it a little bit challenging to use it routinely in clinical practice.

That being said, we do have MRD data predominantly from the European groups that have provided us data using PCR-based testing that could be actionable in the clinical practice if we used it more commonly. I think we also we have newer MRD approaches like cell-free DNA that can get us much greater sensitivity that, hopefully, as those come into the advent of clinical practice, will actually advance the ways that we utilize it.

I typically use MRD in exactly the same way Dr. Ruan mentioned to be able to evaluate the depth of response that you're getting with various regimens and that helps me to judge the relative effectiveness of regimens that can put patients into an MRD negative response. But I think there are many ways that we could use this in the future, both in terms of deciding which patients on BTK inhibitors to discontinue therapy, being able to use time-limited therapy with combinations of novel agents like we're starting to see in CLL, and many other options for approaches for who to take to more aggressive therapies like stem cell transplantation and CAR T-cell. So, I think lots of options out there. None that are really directly actionable in clinical practice today.

Speaker: Yeah. Thank you for the discussion and, and presentation today. In your example of your, of the 68-year-old patient with newly diagnosed MCL, I was missing the option of the VR-CAP, and I was wondering if you can elaborate on that and whether you recommend maintenance with rituximab after VR-CAP.

Dr. Flowers: Yeah. Great question. With the early use of bortezomib in this disease, we had great hope and promise that it would play a role in the management of patients with mantle cell lymphoma or plays a larger role.

It is still an approved agent and that combination regimen of bortezomib-R-CAP dropping the vincristine and, and R-CHOP and replacing with bortezomib is an approved regimen. I would say at least in the United States it's a regimen that is very uncommonly used. And so consequently we don't have much data on its use in clinical practice and there really aren't good data in the same ways that we have data after R-CHOP with maintenance therapy. And so, I don't use the regimen much, so it's hard to comment on whether you should give maintenance after the regimen. But there aren't really data to support that in common practice.

Dr. Ruan: I completely agree. I only want to add that there is sort of institutional practice preference in terms of our strength, and we generally recommend that to our patients. So, VR-CAP we have used it and we have other options that we feel like we can contribute more from our group practice standpoint.
I do want to say that there's more hematological side effects with VR-CAP, for example, to compare with BR-based regimen. And but, you know, the long-term data on the VR-CAP it's quite impressive in terms of improvement in overall survival. But the comparator is R-CHOP, so I feel like it has its role. If it's a community that they don't have bendamustine and other options, then I think VR-CAP would be my choice if the alternative is R-CHOP.

Dr. Flowers: One other comment that I'll make as we're coming to a close, I think one of the things that we have not talked much about is the role of clinical trials in mantle cell lymphoma. And I think given that this is a disease that is or at least is an option for therapy, this is a disease that is still not curable with standard approaches that we use in the frontline or the relapse setting. And I think it is extraordinarily important that when we discuss options for therapy for patients that we discuss clinical trials as a component of that.

You know, more than 30% of our patients who we see with mantle cell now go on clinical trials at least at our center. And I think we view that as a very viable and meaningful option for, for most patients.
So not seeing any further questions, I'll thank you again for joining us today. And thank you all for your time and attention today.

Dr. Ruan: Thank you.