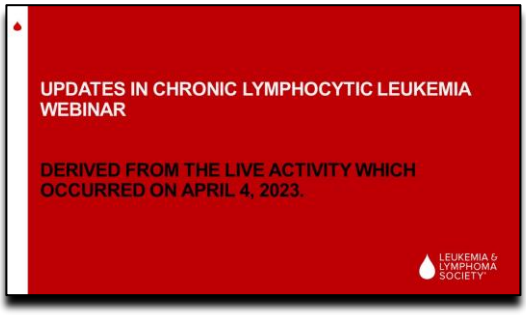
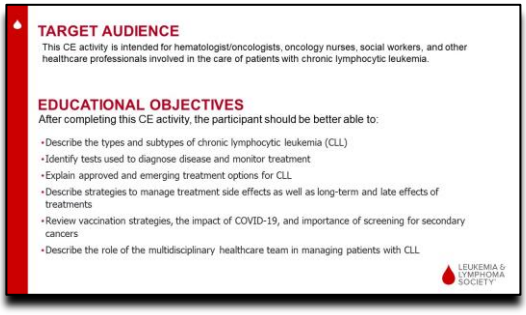


Slide 1: Updates in Chronic Lymphocytic Leukemia

Operator: Greetings and welcome to Updates in Chronic Lymphocytic Leukemia, a web education program. It is now my pleasure to introduce your moderator, Lauren Berger. Thank you, you may begin.

Slide 2: Welcoming Remarks

Lauren Berger: Thank you. On behalf of The Leukemia & Lymphoma Society, thank you for joining us. The Leukemia & Lymphoma Society is committed to improving patient's quality of life through webinars such as this one for healthcare providers, and education and support for patients and caregivers.

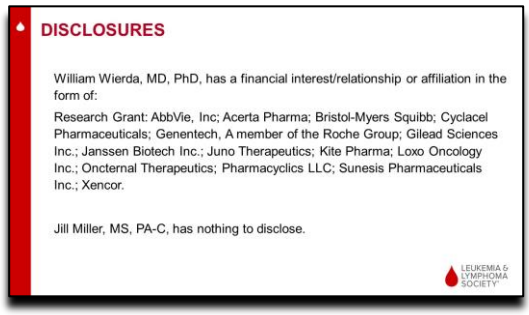


Slide 3: Educational Objectives

The educational objectives are listed on this slide. We will focus on treating CLL, or chronic lymphocytic leukemia, including diagnosis, treatment options, side effect management, the role of the multidisciplinary healthcare team, and resources for you and your patients.

Slide 4: Faculty

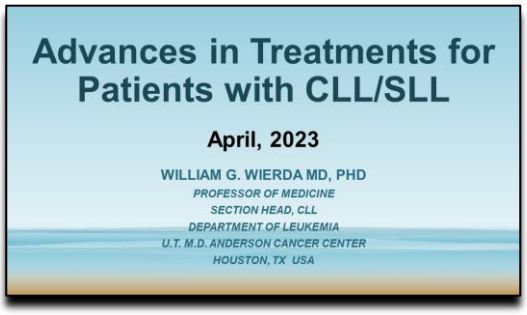
I am now honored to introduce our presenters, Dr. William Wierda, Professor of Medicine and Section Head CLL, Department of Leukemia at the University of Texas MD Anderson Cancer Center in Houston, Texas. And Ms. Jill Miller, Manager Advanced Practice Providers Department of Leukemia at the University of Texas MD Anderson Cancer Center in Houston, Texas. Thank you so much for volunteering your time and expertise.



Slide 5: Faculty Disclosures

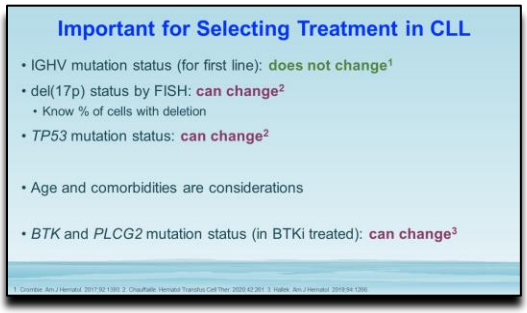
Disclosure information is listed here.

Dr. Wierda, it is now my pleasure to turn the program over to you.



Slide 6: Advances in Treatment for Patients with CLL/SLL

William Wierda: Great. Thank you, Lauren. And thanks to The Leukemia & Lymphoma Society for this support for this program and allowing us to come and talk about chronic lymphocytic leukemia. I'm going to cover therapeutic aspects of chronic lymphocytic leukemia and Jill will be covering several topics that are really more relevant today than ever, some of the things that we do supportive measures for our patients with CLL protection for infection and screening for second cancers etc.

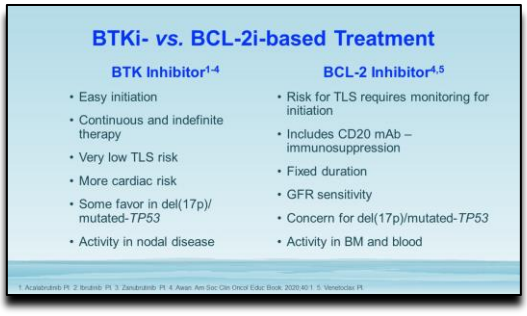


Slide 7: Important for Selecting Treatment in CLL

I'm going to focus on updating and updates from the ASH and recent publications. I'm going to start with some general concepts, one of which is factors that are important to understand and to consider in patients who are needing treatment.

So as you know, patients with chronic lymphocytic leukemia can be monitored and observed for an extended period of time and not need treatment initially, and we only initiate treatments if patients have an indication for treatment. And when they do have an indication for treatment, these are the factors that I like to know for patients because they're helpful in selecting therapy, IGHB mutation status, which doesn't change through the course of the disease. Whether or not a patient has a 17p deletion that's evaluated by FISH, that can change with treatment, particularly patients can acquire high risk features. Whether or not TP-53 is mutated, so that's done by TP-53 mutation plus the assessment or sequencing of the TP53 gene.

It's important to take into consideration patients age and comorbidities and for previously treated patients, particularly patients who have been on a BTK inhibitor, sequencing and determining whether or not BTK or PLCgamma2 are mutated is an important feature and that can be acquired through exposure to the BTK inhibitors that we currently have available.



Slide 8: BTKi- vs. BCL-2i-based Treatment

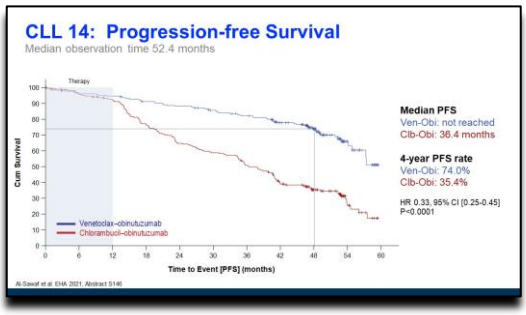
Now, in terms of frontline therapy, this slide is important because it summarizes the two strategies that we can take in terms of first treatment for patients. We have options and those options are BTK inhibitor-based therapy, or Bcl-2 inhibitor based therapy.

So we'll start first with BTK inhibitor based therapy. We have three agents that are currently approved that are BTK inhibitors, those are all covalent, irreversible inhibitors of BTK. Ibrutinib was the first available and then the second generation available BTK inhibitors include acalabrutinib and zanubrutinib. Those are extremely effective drugs at controlling disease, reducing the bulk of disease, eliminating patient symptoms, but they don't get patients in a deep remission and so they're given continuously until disease progression. When patients first start on treatment with the BTK inhibitors, we usually see an elevation in the white count. So the white count will go up transiently, and then go back down and lymph nodes typically will shrink right away when patients first go on treatment.

The BTK inhibitors do work and have activity in patients with high-risk features, including 17p deletion and mutated TP53, that are particularly effective at shrinking nodal disease, less potent that eliminating circulating disease and disease in the bone marrow. That's in contrast to the Bcl-2 inhibitor. We have one agent currently available, which is Venetoclax. Venetoclax, is a very potent drug at inducing apoptosis to the point where we have to start at a low dose and ramp the dose up over four to five weeks to eliminate

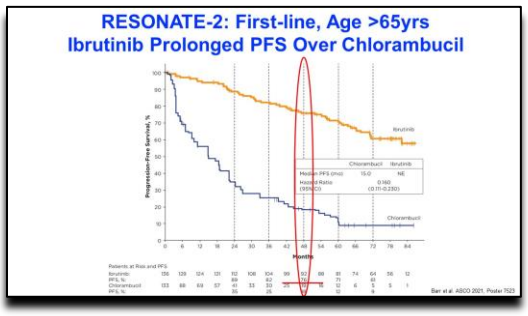
the risk or reduce the risk for tumor lysis syndrome, which you can see in patients if you don't follow the typical or recommended ramp up.

The target dose is 400 milligrams daily, and Venetoclax is typically given with a CD20 antibody. We have to be careful for patients who have renal insufficiency, patients who have a large bulk of disease because that does increase their risk for tumor lysis. And this drug does have significant activity in patients with high risk features, including 17p deletion and mutated TP53. It's highly effective at clearing disease from the blood and from the bone marrow, which is complementary to the BTK inhibitors and one of the rationales for combining these agents, and I'll talk a little bit about that in some of the data that I'm going to show you.



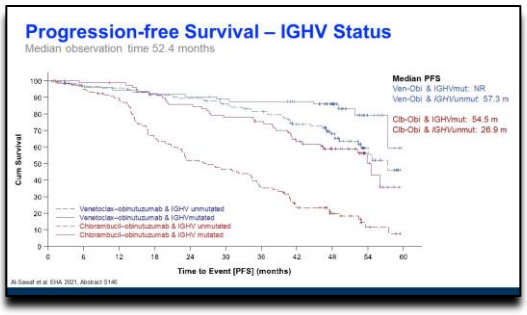
Slide 9: CLL 14: Progression-free Survival

CLL14 was the first trial that led to approval of Venetoclax in the frontline setting. Venetoclax, as I mentioned, is a potent drug. It achieves a high rate of complete remission and undetectable, measurable or minimal residual disease by a year of treatment. So it's given as a fixed duration of treatment. Patients get 12 cycles, or one year of Venetoclax as frontline therapy, two years in the relapse setting, and that's typically given in the frontline setting with obinutuzumab, six cycles. This is the outcomes for the CLL14 trial, comparing Venetoclax based therapy in the blue curve with chemo immunotherapy in the red curve, and you can see superior progression free survival for patients who receive Venetoclax plus obinutuzumab versus chlorambucil and obinutuzumab with at 48 months, about 75% of patients being progression free.



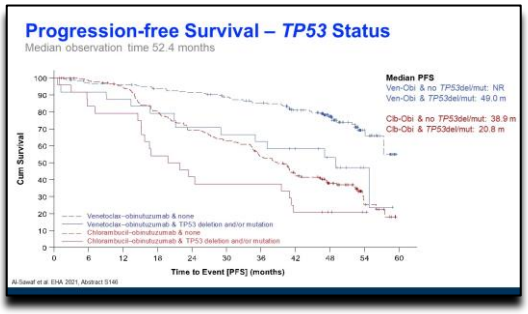
Slide 10: RESONATE-2: First-line, Age >65yrs Ibrutinib Prolonged PFS Over Chlorambucil

Now, that's important because the other option for treatment is the BTK inhibitor, and this is data from the RESONATE-2 trial with ibrutinib in the frontline setting in the orange curve. And you can see that at four years of continuous treatment with ibrutinib, about 75% of the patients are progression free in that setting. So similar progression free outcomes if you're looking across these phase three clinical trials, the difference here again is the continuous and indefinite treatment with ibrutinib versus one year of treatment with a Venetoclax based therapy.



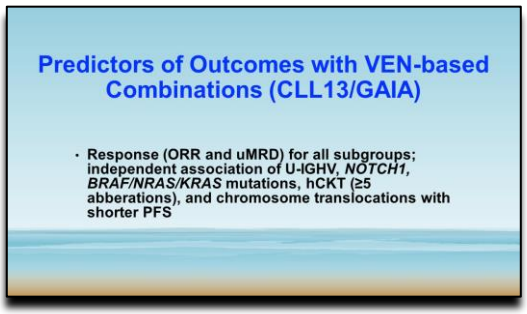
Slide 11: Progression-free Survival – IGHV Status

Going back to Venetoclax based therapy, looking at factors that correlate with outcomes, IGHV mutation status does correlate with progression free survival, as you can see here, in comparing the blue curves. The solid blue curve being patients who have mutated immunoglobulin gene, the dashed blue curve being those patients who have an unmutated immunoglobulin gene who received Venetoclax based therapy. So shorter progression free survival for patients with fixed duration treatment who have an unmutated immunoglobulin gene.



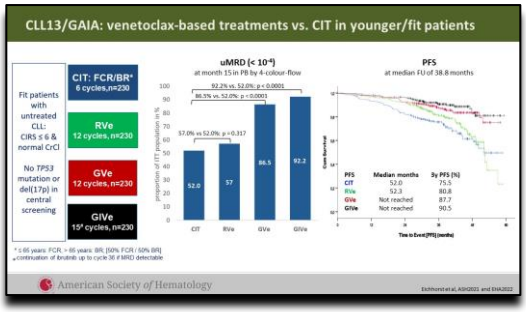
Slide 12: Progression-free Survival – TP53 Status

Also shorter progression free survival for patients who have an abnormal TP53. Those patients are shown in the solid blue curve versus the patients who have a wild type or normal TP53 gene who receive Venetoclax in the dashed blue curve.



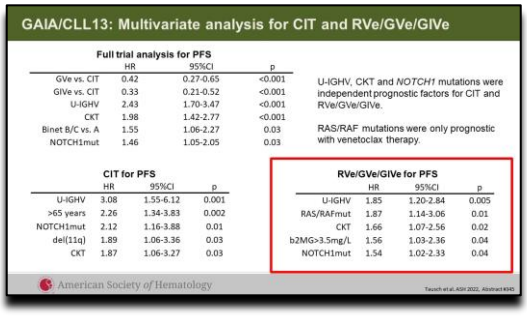
Slide 13: Predictors of Outcomes with VEN-based Combinations (CLL13/GAIA)

So there was an abstract that was presented, a couple of abstracts actually that were presented at ASH that summarize the CLL13 trial done by the German CLL study group. And that trial, the CLL13 trial had four treatment arms. It was a randomized frontline trial.



Slide 14: CLL13/GAIA: venetoclax-based treatments vs. CIT in younger/fit patients

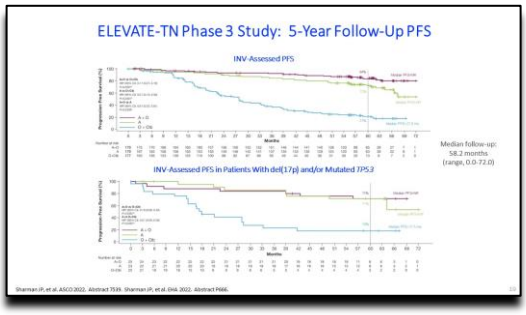
One arm of patients received chemo immunotherapy either FCR or bendamustine rituximab. Shortest progression free survival was associated with those patients who receive chemo immunotherapy. And then there were three Venetoclax based treatment arms. The green curve shows Venetoclax plus rituximab, and you can see an inferior progression free survival with rituximab in this setting, versus obinutuzumab with Venetoclax, which are those patients in the red curve, or a triplet of ibrutinib, Venetoclax and obinutuzumab, and those are patients in the black curve.



Slide 15: GAIA/CLL13: Multivariate analysis for CIT and RVe/GVe/GIVe

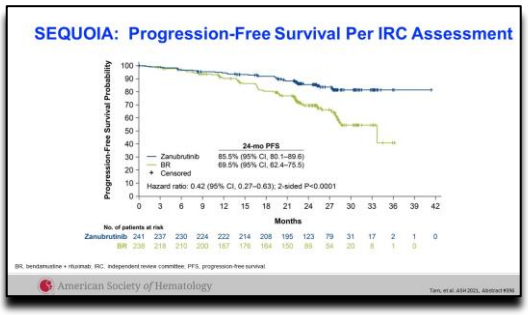
And what they reported in this abstract was outcomes associated--factors that associated with improved progression free survival or shorter progression free survival.

In the red box, you can see a shorter progression free survival associated with those patients who have an unmutated immunoglobulin gene with mutations in the RAS gene or the RAF gene, complex karyotype, elevated beta-2 microglobulin and notch one mutation. Now, this trial did not enroll patients with 17p deletion. I would anticipate that 17p deletion or mutated TP53 would be included on this list, had those patients been enrolled on this study.



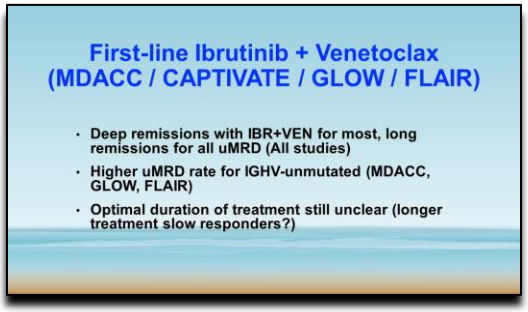
Slide 16: ELEVATE-TN Phase 3 Study: 5-Year Follow-Up PFS

Now, that's fixed duration Venetoclax base. If we look the patients who receive a BTK inhibitor based therapy, acalabrutinib and a second generation BTK inhibitor, the progression free survival with a longer term follow up is shown on the top by treatment arm in this phase three randomized trial so you can see best progression free survival in the magenta curve for patients who received acalabrutinib plus obinutuzumab. In green are patients who received acalabrutinib monotherapy, and that's compared with chemo immunotherapy, again chlorambucil obinutuzumab. And you can see very good outcomes for patients with 17p deletion on the lower curve.



Slide 17: EQUOIA: Progression-Free Survival Per IRC Assessment

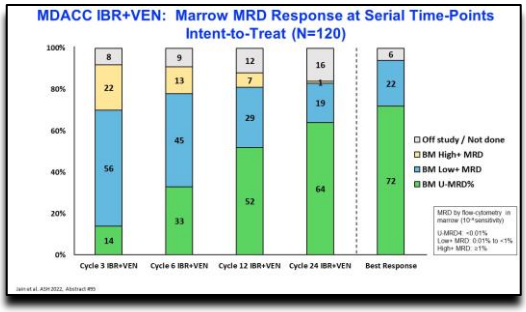
The SEQUOIA trial evaluated zanubrutinib, another inhibitor of BTK. This was a phase three randomized trial that did not include patients with 17p deletion. The blue curve indicates patients who receive zanubrutinib monotherapy versus the green curve which represents patients who received BR in the frontline setting. So superior outcomes with zanubrutinib over chemo immunotherapy.



Slide 18: First-line Ibrutinib + Venetoclax (MDACC / CAPTIVATE / GLOW / FLAIR)

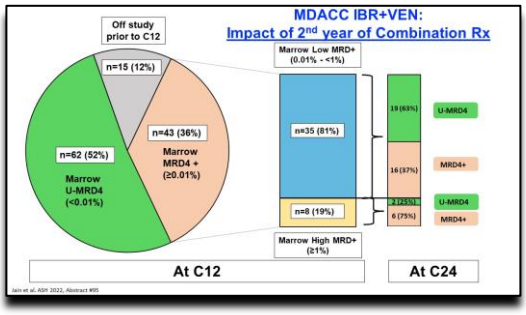
Now, we have looked at combined ibrutinib plus Venetoclax at MD Anderson and in a cohort of 120 patients. Other trials have evaluated that combination, the CAPTIVATE trial, the GLOW trial is a phase three trial, and then the FLARE trial. These were all updated at ASH, and the summary for the updates is shown in those bullets below. Very high undetectable MRD rate with this combination. And pretty much all the subgroups of patients similarly respond with high undetectable MRD rates.

Now, there was a higher undetectable MRD rate shown for patients who have an unmutated immunoglobulin gene, which is a surprising feature. And the GLOW trial reported a shorter progression free survival for those patients. So undetectable MRD status needs to be taken in context with a patient population that's being reported on and IGHV mutation status, particularly with fixed duration treatment does still correlate with shorter progression free survival for patients who have an unmutated immunoglobulin gene, particularly on the GLOW trial. The optimal duration of treatment is still yet to be determined.



Slide 19: MDACC IBR+VEN: Marrow MRD Response at Serial Time-Points Intent-to-Treat (N=120)

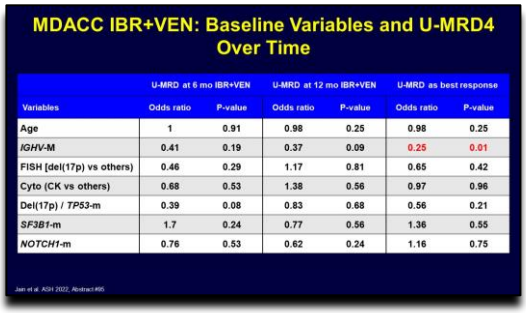
So these are our data from Anderson with three months of ibrutinib monotherapy followed by 24 cycles of combined ibrutinib plus Venetoclax. These are a bone marrow undetectable MRD rates, 64% at the end of 24 cycles of combined therapy, 72% undetectable overall, which is a very high rate of undetectable MRD including in a frontline setting, higher than what we had seen previously with chemo immunotherapy.



Slide 20: MDACC IBR+VEN: Impact of 2nd year of Combination Rx

The important point with this updated data is that patients do continue to improve their response with continued therapy. If you look for example, at the end of cycle 12, the salmon colored portion of that diagram represents patients who are still detectable for MRD at the end of 12 cycles. If those patients continue treatment for another year of combined therapy, you see about a 50% conversion rate undetectable with that continued treatment.

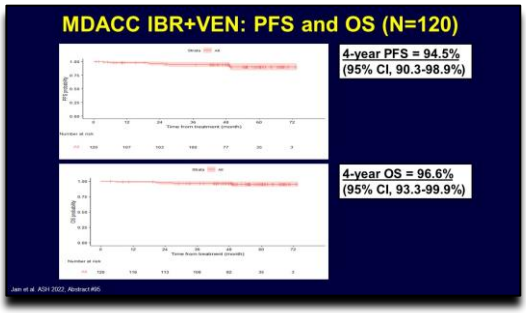
We modified this trial later to allow for a third year of treatment for patients who are still MRD positive at the end of two years. And in that setting, we also see about a 50% conversion rate with that additional third year of treatment.



	U-MRD at 6 mo IBR+VEN		U-MRD at 12 mo IBR+VEN		U-MRD as best response	
Variables	Odds ratio	P-value	Odds ratio	P-value	Odds ratio	P-value
Age	1	0.91	0.98	0.25	0.98	0.25
IGHV-M	0.41	0.19	0.37	0.09	0.25	0.01
FISH [del(17p) vs others)	0.46	0.29	1.17	0.81	0.65	0.42
Cyto (CK vs others)	0.68	0.53	1.38	0.56	0.97	0.96
Del(17p) / *TP53*-m	0.39	0.08	0.83	0.68	0.56	0.21
SF3B1-m	1.7	0.24	0.77	0.56	1.36	0.55
NOTCH1-m	0.76	0.53	0.62	0.24	1.16	0.75

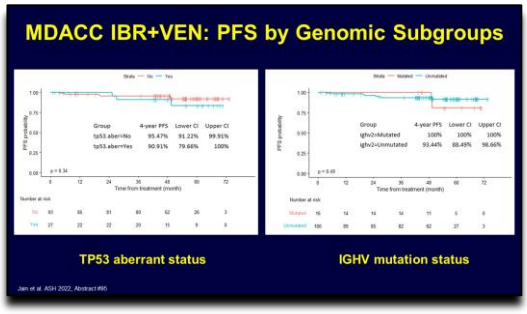
Slide 21: MDACC IBR+VEN: Baseline Variables and U-MRD4 Over Time

We were looking for features that correlated with undetectable MRD status. As I mentioned, undetectable MRD was higher among those patients who have an unmutated immunoglobulin gene. That was seen in our data, and it was seen in the other trials.



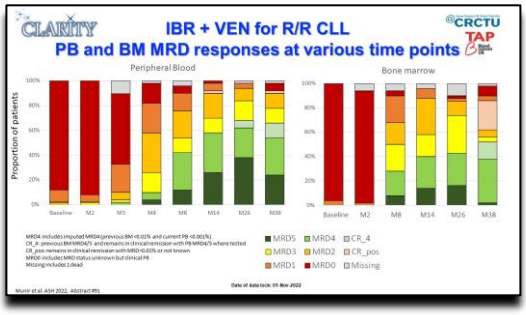
Slide 22: MDACC IBR+VEN: PFS and OS (N=120)

Now, unlike the GLOW trial, the GLOW trial particularly, our trial allowed for two to three years of treatment. So that does, I think, some wide impact on results that we observe and outcomes for our patients. But you can see at four years, progression free survival at 94.5% overall survival at 96.6% are very high and this is a high risk population of patients. The inclusion criteria require patients to have an unmutated immunoglobulin gene, or 17p deletion or 11q deletion etc. So, they were selected for high risk features. And as you can see here, we're seeing exceptionally good outcomes with this combined therapy.



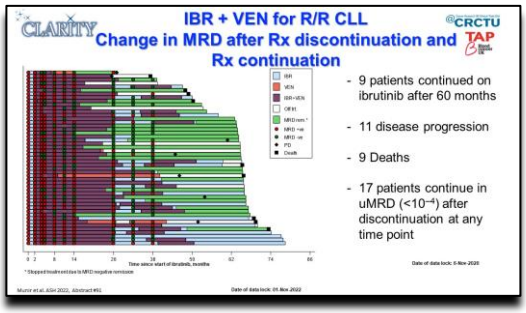
Slide 23: MDACC IBR+VEN: PFS by Genomic Subgroups

So far with the current follow up that we have, the curves are not separating by TP53 status on the left or by IGHV mutation status on the right. Again, this is fixed duration treatment. I do expect with longer term follow up that we will probably see those curves separate but we'll need to do the follow up.



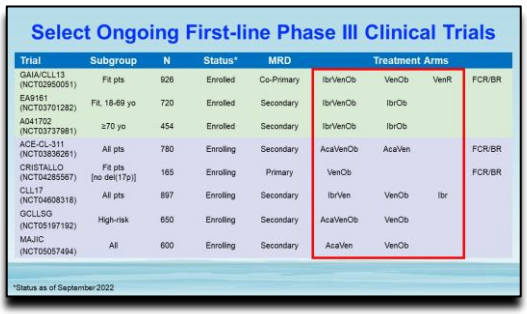
Slide 24: IBR + VEN for R/R CLL PB and BM MRD responses at various time points

This combination has been studied in the clarity trial by the UK group. So again, ibrutinib monotherapy to debulk and then combined ibrutinib plus Venetoclax. On this trial, patients could receive up to two years of treatment. On the left, you can see blood undetectable MRD, on the right, bone marrow undetectable MRD in green for these previously treated patients. So usually, the response rates and the progression free survival are inferior in the relapse setting. But as you can see here, very good, very high undetectable MRD rates for this previously treated population of about 50 patients, most of whom had prior chemo immunotherapy but very good outcomes for those patients. So, as I mentioned here, the green indicates undetectable MRD status in blood or bone marrow



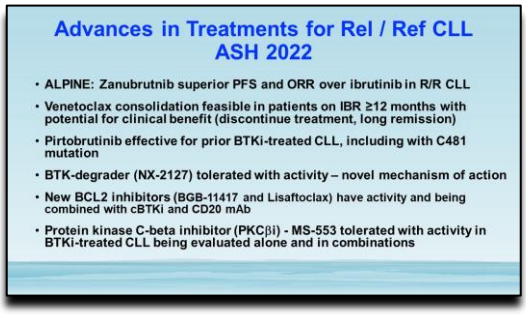
Slide 25: IBR + VEN for R/R CLL Change in MRD after Rx discontinuation and Rx continuation,.

If you follow the green on the swimmer plot, you can see that many of those patients who achieved undetectable MRD status are maintaining that status with longer term follow up. Again, in a relapsed population of patients, these are exceptionally good outcomes.



Slide 26: Select Ongoing First-line Phase III Clinical Trials

So a number of frontline clinical trials either ongoing or have enrolled that we'll be comparing different combination arms of treatment with BTK plus Bcl-2, BTK plus CD20 antibody, Bcl-2 plus CD20 antibody, some of which also include as you can see to the far right, chemo immunotherapy comparator arms for these phase three trials. But over the next three to five years, I will say that we'll probably have a little bit better idea what optimal combinations to use for treating patients and what outcomes to expect for those patients.

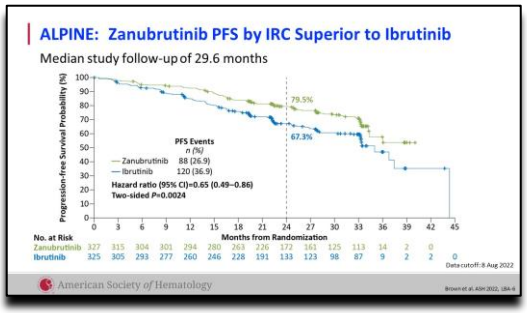


Slide 27: Advances in Treatments for Rel / Ref CLL ASH 2022

In the next few minutes, I want to go over relapsed disease and outcomes for relapse particularly paying attention to what was presented at ASH.

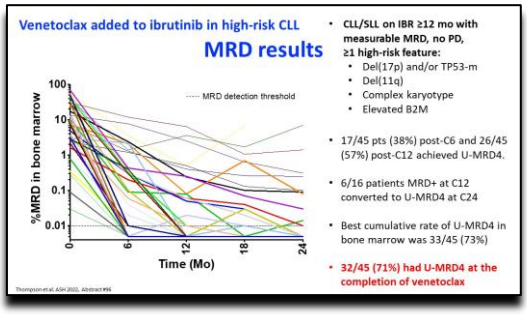
Slide 28: ALPINE: Zanubrutinib PFS by IRC Superior to Ibrutinib

There is a randomized phase three trial of ibrutinib versus zanubrutinib for relapsed patients, which was recently updated. The incidence of side effects and toxicities particularly atrial fibrillation was higher with ibrutinib compared to zanubrutinib on this trial and in the early report. And then the more recent report progression free survival was updated, and you can see improved progression free survival for patients who received zanubrutinib in the green curve, versus ibrutinib in the blue curve. That held also for patients with 17p deletion mutated TP53.



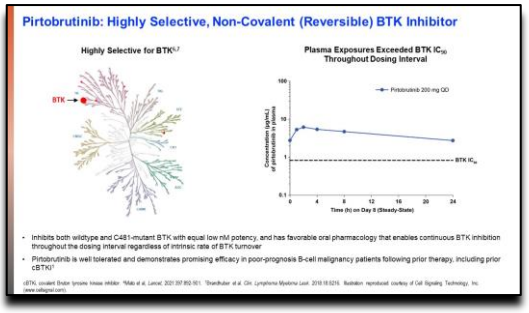
Slide 29: ALPINE: Zanubrutinib Improved PFS in Patients with del(17p)/TP53mut

So these data suggests that improve outcomes of zanubrutinib over ibrutinib in terms of progression free survival.



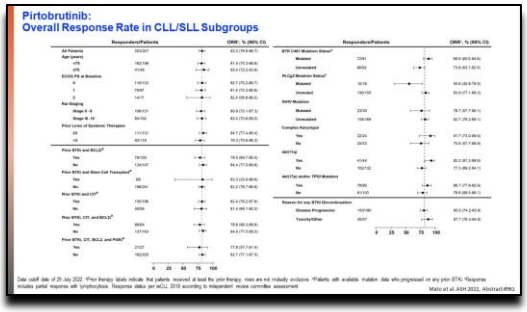
Slide 30: Venetoclax added to ibrutinib in high-risk CLL- MRD results

We reported on a trial that we've been doing with consolidation with Venetoclax for patients who still have measurable residual disease who have been on a BTK inhibitor for at least a year or longer. So this strategy is adding Venetoclax to patients who have been on a BTK inhibitor with the goal of getting patients undetectable and getting them off treatment. In this updated data Phillip Thompson presented, you can see the bottom line on the right at the bottom, in the red text, 71% of patients had converted to undetectable MRD at the completion of their plans, Venetoclax based therapy. This manuscript is currently in press, and you'll be able to read more about it in the near future.



Slide 31: Pirtobrutinib: Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

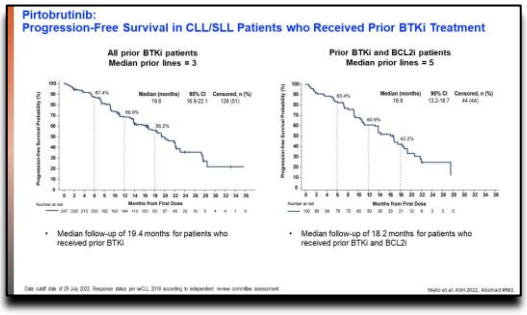
Pirtobrutinib was updated at ASH for the BRUIN study. Pirtobrutinib is a non-covalent reversible inhibitor of BTK oral drug that's highly selective for BTK. As you can see, on the left, that one dot there, the largest one died at about the 10:00 position is BTK. There's very little off target, and that is reflected really in the toxicity and tolerability profile that we have seen with pirtobrutinib. It's an extremely well tolerated drug. It's dosed once a day, at 200 milligrams daily.



Slide 32: Pirtobrutinib: Overall Response Rate in CLL/SLL Subgroups

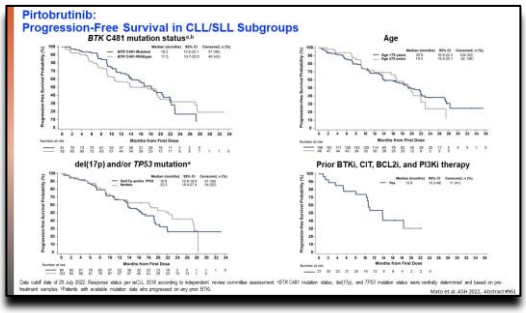
And the updated ASH was looking at pirtobrutinib in patients who had had prior BTK inhibitor, and there were about 247 patients, most of whom were refractory to prior BTK. About 77%, I believe of those patients had progressed on prior BTK. 90% of them had had prior ibrutinib, so most of them had prior ibrutinib. About 10% had had prior acalabrutinib. And there were just a few patients who had had zanubrutinib.

The response rates are shown in this slide and the overall response rate is about 80%. And patients had similar responses across the subgroup analyses. So 80% response rate among those patients who had had a mutation in BTK, the C481 mutation, patients who had progressed on prior BTK etc. So very good activity in terms of or their responses across the subgroups, including in patients who had failed prior BTK.



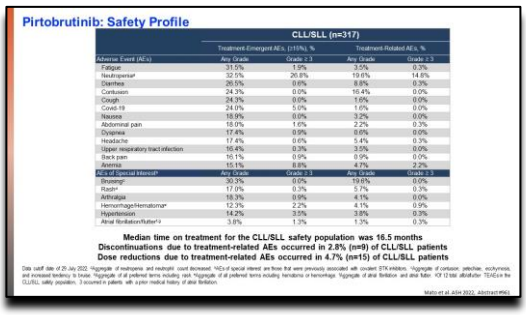
Slide 33: Pirtobrutinib: Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

On the left, the median progression free survival, reported in this update for all those patients was about 20 months, so 19.6 months. And on the right, you can see the median progression free survival of about 17 months for patients who had had prior BTK and Bcl-2 inhibitor based therapy.



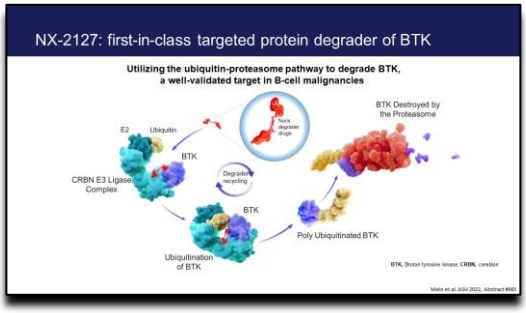
Slide 34: Pirtobrutinib: Progression-Free Survival in CLL/SLL Subgroups

And as I mentioned, responses as well as a similar progression free survival among those patients who are considered high risk, those who had a BTK mutation or 17p, mutated TP53, etc.



Slide 35: Pirtobrutinib: Safety Profile

Very safe drug, no dose limiting toxicity or maximum tolerated dose identified in the phase one portion. So these patients are tolerating this drug extremely well.

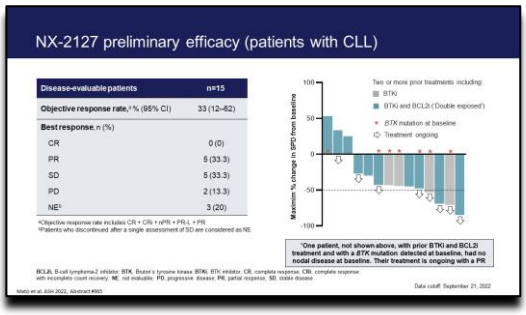


Slide 36: NX-2127: first-in-class targeted protein degrader of BTK

The next drug that was reported on is NX2127. This drug binds to BTK and causes BTK degradation. It also binds to cereblon and causes degradation, and so it has two functions, really. It functions as a BTK degrader, as well as a cereblon degrader. And this drug has been studied in a phase one cohort of patients that were reported on at ASH.

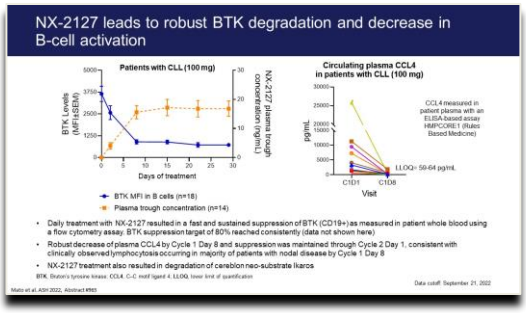
Slide 37: NX-2127 safety summary (all participants) by dose

These are the side effects and toxicities associated with NX2127. There were three dose levels evaluated, 100 milligrams daily, 200 milligrams daily, 300 milligrams daily. There had been some cases of atrial fibrillation reported, as you can see, 17% overall and the escalation was held, and de-escalation and expansion of the 100 milligram cohort is currently ongoing.



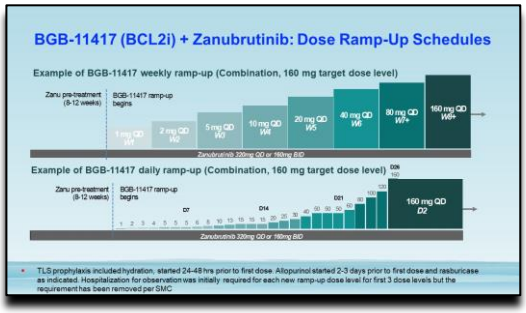
Slide 38: NX-2127 preliminary efficacy (patients with CLL)

There has been activity reported with this drug. As you can see on the left, most for a response had a pro remission, about a third of them, in fact, and you can see reduction in lymph nodes, the right, with waterfall plot.



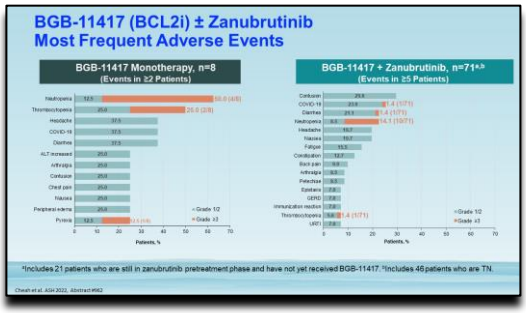
Slide 39: NX-2127 leads to robust BTK degradation and decrease in B-cell activation

The patient's had sampling of their leukemia cells while on drug and this slide shows elimination of BTK, and on treatment with exposure to this degrader.



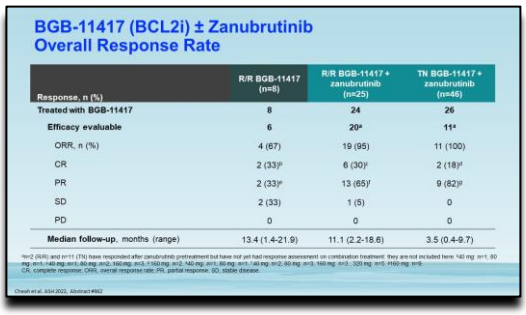
Slide 40: BGB-11417 (BCL2i) + Zanubrutinib: Dose Ramp-Up Schedules

There were two Bcl-2 inhibitors reported on at ASH. One is this one developed by Beijing which is BGB11417. That drug is evaluated as monotherapy as well as in combination. This shows you the ramp up for BGB1417. There is a weekly ramp up on top and then a daily ramp up on the bottom to avoid tumor lysis syndrome.



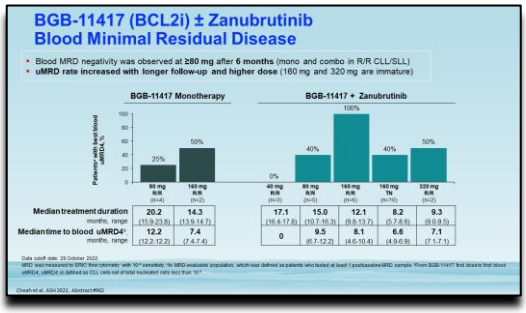
Slide 41: BGB-11417 (BCL2i) ± Zanubrutinib Most Frequent Adverse Events

There have been a number of patients treated with this compound, eight with monotherapy but 71 reported here with combined with zanubrutinib. No signals that were not unanticipated in terms of safety. Neutropenia, as you can see there on the left, was reported as well as thrombocytopenia, which we have seen also with the other approved Bcl-2 inhibitor Venetoclax.



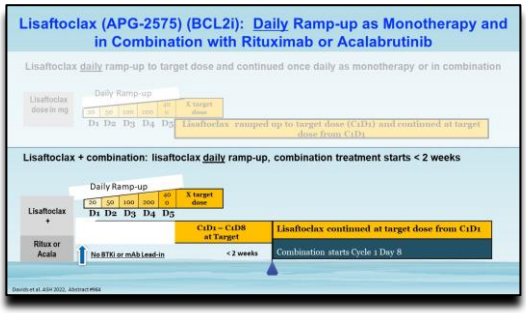
Slide 42: BGB-11417 (BCL2i) ± Zanubrutinib Overall Response Rate

Activity with this compound, as you can see here, complete responses in about a third of the patients who received monotherapy and in combination also, about a third of them had had complete remission.



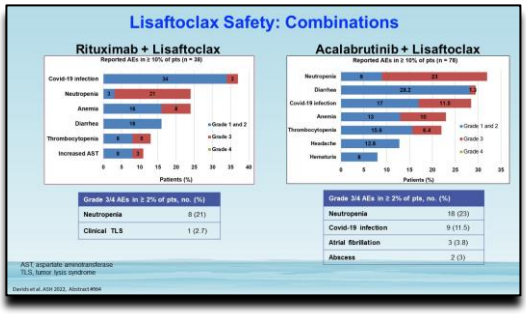
Slide 43: BGB-11417 (BCL2i) ± Zanubrutinib Blood Minimal Residual Disease

Overall, high response rate with the combination, and undetectable MRD status achieved with monotherapy as well as with combination.



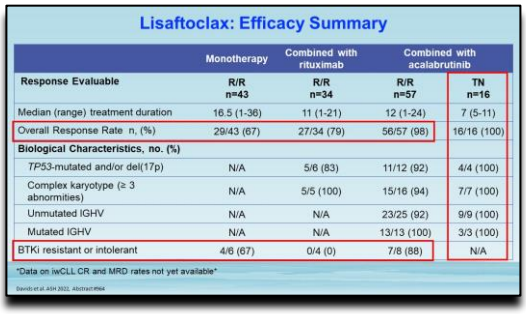
Slide 44: Lisaftoclax (APG-2575) (BCL2i): Daily Ramp-up as Monotherapy and in Combination with Rituximab or Acalabrutinib

The other drug, that's the Bcl-2 inhibitor that's under investigation.. is this Lisaftoclax, and that was evaluated as monotherapy as well as combined with acalabrutinib or rituximab. You can see here, a rapid ramp up strategy daily over five days and then the drug was combined at the target dose with, as I mentioned, rituximab or acalabrutinib.



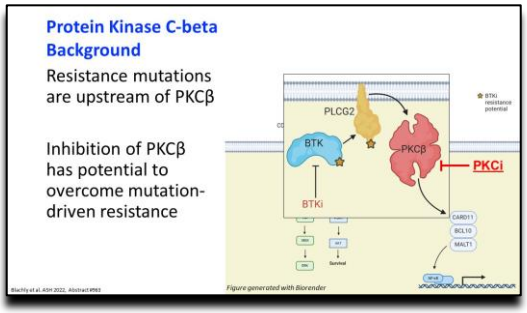
Slide 45: Lisaftoclax Safety: Combinations

No safety signals. Again, neutropenia seen with this compound, which has been seen with other Bcl-2 inhibitors. But overall, a well-tolerated drug.



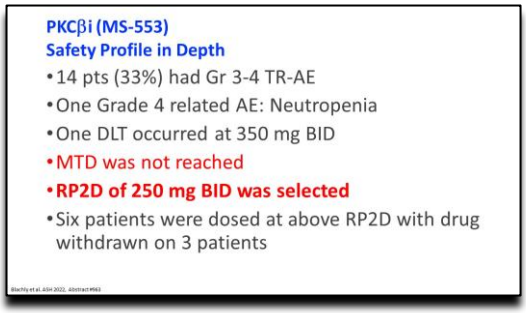
Slide 46: Lisaftoclax: Efficacy Summary

With activity, you can see a number of patients treated here with monotherapy 43 and the response rate of two thirds of those patients responding to treatment, and then also activity and tolerability in combination with rituximab and with acalabrutinib in the relapse setting, as well as in the frontline setting.



Slide 47: Protein Kinase C-beta Background

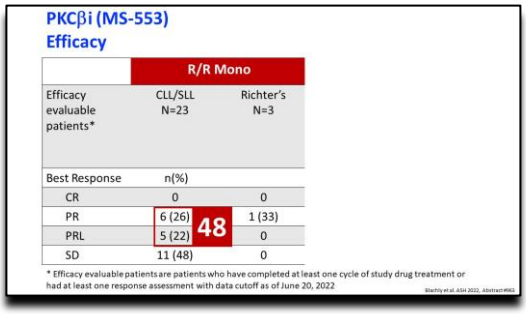
And then finally, the last compound that I wanted to touch on is a new drug, a new category of drug that inhibits protein kinase C beta. So protein kinase C beta is a molecule that is downstream of the B cell receptor signaling pathway. You can see it in the salmon color, protein in the cartoon to the right.



Slide 48: PKCbi (MS-553) Safety Profile in Depth

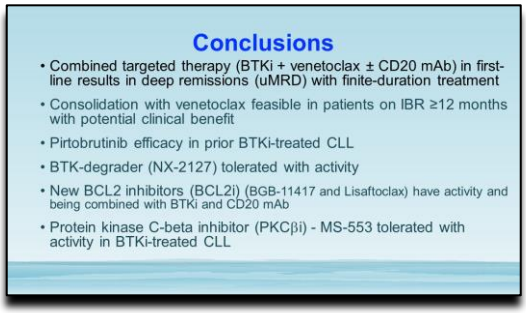
And so MS553 is the name of the compound that is the protein kinase C beta inhibitor and was evaluated in dose escalation early cohort, and it's also now in study in combination.

So you can see there, 14 patients treated. About a third of them had a grade three or four treatment emergent adverse event. There was one grade four neutropenia. Maximum tolerated dose had not been reached, and the recommended phase two dose was 250 milligrams twice a day. This also is an oral compound and is being studied, as I mentioned, in mono therapy, but also in combination.



Slide 49: PKCbi (MS-553) Efficacy

And it's also being evaluated for patients with Richter's transformation. You can see there is some activity, early activity identified with the first 23 patients reported. 48% is the response rate. And as I mentioned, it's being evaluated in combination. And you can see from this table, just a handful of patients treated with combined acalabrutinib or combined Venetoclax based therapy.



Slide 50: Conclusions

So this is my last slide and reviews the conclusions. There's a lot of activity going on in CLL. We're very excited about our frontline combinations and the depth of remission we're seeing, the long responses that we're seeing. We do still see resistance, and we're enthusiastically moving forward with some new agents that should have activity and hold promise for those patients who have failed standard treatment, and those include the degraders as well as protein kinase C beta inhibitor.

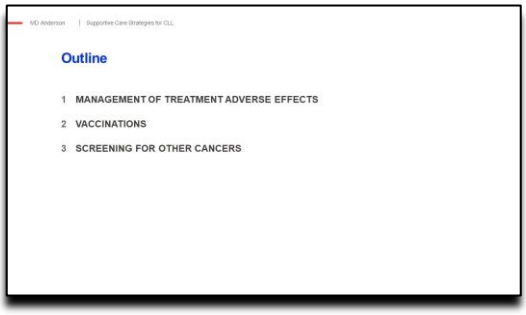
Slide 51: Thank you!

So with that, I will thank you for your attention and I'm happy to turn over to Jill.

Jill Miller: All right. Thank you, Dr. Wierda.

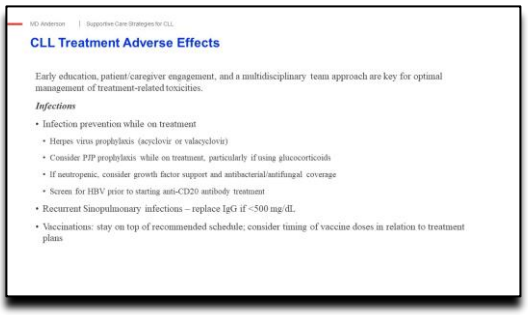
Slide 52: Supportive Care Strategies for CLL

So my section of the program today will include supportive care strategies for CLL. And as Lauren mentioned earlier, I am a Physician Assistant at MD Anderson. I'm the manager of our outpatient team of APPs. There's about 35 of us and growing. So I'm happy for the opportunity to be here today.



Slide 53: Outline

So our outline of what we're going to cover in this part of the talk is management of treatment adverse effects. We're going to talk briefly about vaccinations and then screening for other cancers.



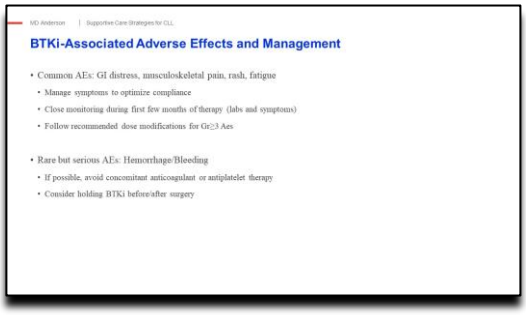
Slide 54: CLL Treatment Adverse Effects

So first talking about treatment of adverse effects. I'll lead with saying that the key to optimal management of adverse effects is education, ongoing education, ongoing interaction with the patient as well as their caregivers, so that they know what to expect, they know what is serious versus something that can be managed through and continuous follow up as they go through treatment. A multidisciplinary team approach is also key. That includes in our clinic, we have usually an APP and a physician. Seeing patients, we have a team of pharmacists who are also involved, and an oral oncology drug management program. And we engage other team members as needed to continuously support our patients through treatment.

So the first adverse effect I wanted to talk about is infections. This is universal no matter what type of treatment you're looking at for CLL. Infection is always a top concern. And so we'll talk about infection prevention while patients are on treatment. This for us always includes prophylaxis for herpes virus, either with Acyclovir or Valacyclovir, and this is regardless of whether or not they have had the Shingrix vaccination. While they're on treatment, we still provide these oral therapies. They're very well tolerated. They cause very little toxicity. So we include those for the duration. And usually about six months following treatment, they stay on these medications.

PJP prophylaxis is not something we routinely use with all of our patients, but in those who are particularly immunosuppressed, especially if they have been using or are on glucocorticoids, either for autoimmune cytopenia or some other reason, then we'll add in PJP prophylaxis while they're on treatment. Neutropenia is something that we see a lot, especially with Venetoclax based therapies, and we use growth factor a lot to bring this up. If they are chronically, persistently neutropenic, then we might add anti-bacterial and anti-fungal coverage as well. And then in another slide we'll talk more about CD20 antibody treatment, but we always want to screen patients who are about to start CD20 treatment for HPV. And as I said, we'll talk about that in more detail in just a minute.

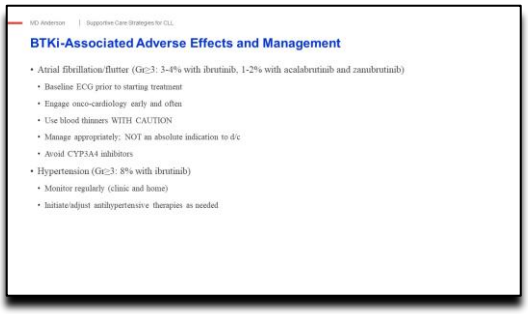
Then, for patients who have recurrent, especially spinal pulmonary infections, you want to monitor their IgG levels and consider replacement if their IgG level is below 500. If it's below 500, and they're not having recurrent infections, it's not as much of an issue and it's not as much of a priority to replace, but certainly, in those patients who have recurrent infections that can be really beneficial. And then vaccinations, just as part of our ongoing education with our patients, we make sure they understand the importance of vaccinations and staying on top of their recommended schedule, the timing of vaccine doses, you don't always have the luxury of timing the vaccine doses around treatment, but if at all possible, to do those vaccine doses as far away from treatment, especially around CD20 antibody treatment.



Slide 55: BTKi-Associated Adverse Effects and Management

So next, adverse effects I wanted to cover are those that are associated with BTK inhibitor therapy. The common adverse effects that we see, for the most part, we try to manage through those initially as opposed to holding or dose reductions. So these include GI distress, musculoskeletal pain, rash, and fatigue are commonly reported. So if you can educate your patients upfront that these are possible side effects that they might experience and help them understand strategies to deal with these. And we can oftentimes keep them on therapy, keep them at the optimal dose, and manage these, especially these tend to be most significant during the initial months of therapy, and so we closely monitor patients as they start therapy. Of course, we're going to be monitoring their labs for the expected lymphocytosis but we're also closely monitoring for their tolerance as they get started. And then if these common adverse effects are persistent or severe, then we would follow the recommended dose modifications, which are basically to hold, let it resolve to a great one and then resume at a lower dose.

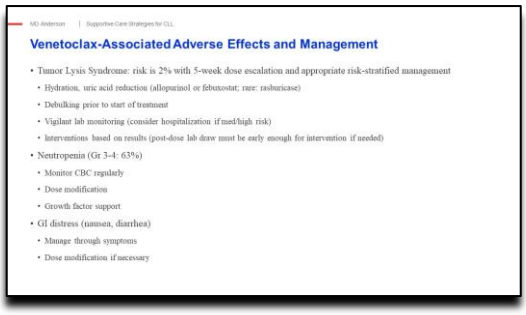
Next, I'll talk about some of the more serious adverse effects to be concerned about with BTK based therapy. The first is hemorrhage and bleeding. This is a very commonly reported as adverse effect. And so if at all possible, you want to avoid concomitant anticoagulant or antiplatelet therapy. If they're already on those therapies before you start treatment, then it's a good idea to consult either a hematologist or a cardiologist for optimal management. Also, you want to consider instructing patients to hold their BTK inhibitor before and after surgery, anywhere from three days for something simple starting one day prior to the procedure, to up to 10 to 14 days if it's a major surgery with a high risk of bleeding. And usually, the procedure would take place kind of midway in that whole period.



Slide 56: BTKi-Associated Adverse Effects and Management

Atrial fibrillation is another concern with BTK based therapy. The incidence of grade three or above atrial fibrillation seems to be somewhat higher with ibrutinib, but it also is noted with the other two BTK inhibitors as well. So you want to do a baseline ECG prior to the initiation of treatment, so you can identify those that may have an undiagnosed cardiac arrhythmia. If you do see atrial fibrillation emerge or patients report having palpitations that you can't quite confirm, you want to engage cardiology early on in the process so that they can do a Holter monitor, see what the frequency is of these events and engage them from management early on. Again, using blood thinners with caution due to the increased risk of bleeding and bruising.

Atrial fibrillation is not an absolute indication to discontinue treatment with BTK inhibitors. If it can be managed, if it can remain a grade one or two, then they can remain on therapy. The important thing is to control the rate and also minimize the risk of clot. And then of course, avoiding CYP3A4 inhibitors, which increase the concentration of the BTK inhibitors and thus would increase their chance of having these adverse effects. Hypertension is another adverse effect this concern with BTK inhibitors in particular with ibrutinib as reported at roughly an 8% incidence with ibrutinib. You want to instruct patients to monitor their blood pressure regularly. When they come to clinic, they may have white coat syndrome. They may have an elevated blood pressure, but it's important to know what their blood pressure is running at home as well. So again, education is key. And then managing the hypertension. Again, this is not an absolute indication to switch therapy but to either initiate or adjust or antihypertensive therapies as needed.

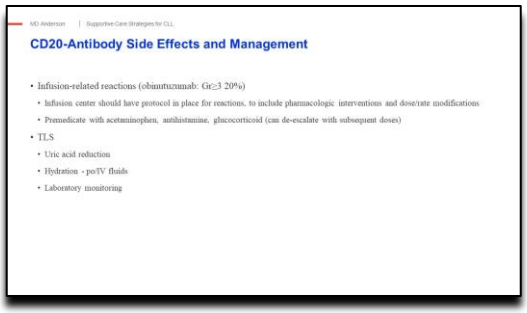


Slide 57: Venetoclax-Associated Adverse Effects and Management

Moving on to Venetoclax associated adverse effects. As Dr. Wierda discussed earlier, tumor lysis is a big concern. If the standard five week dose escalation and risk management is followed, the risk is very minimal at 2%. So hydration is important, education is important. I like to tell patients that this period of their treatment is their bootcamp. It's tedious. It's a lot of back and forth. It's a lot of lab draws. But if they understand the risk of tumor lysis, what that means and what can happen if it goes undetected, they generally are very receptive to complying with the schedule.

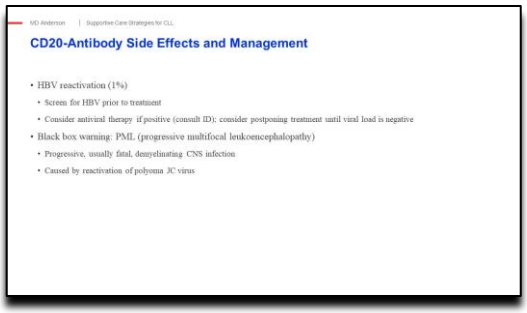
Some patients if they're considered high risk should be admitted for at least the first two dose escalations to monitor more closely for tumor lysis. And there is some benefit in debulking prior to the start of Venetoclax to really reduce their risk of TLS. And then one thing that's important to note is that you not only have to schedule the labs, but you also have to time the lab draws so that someone is present to look at those results and act on them. They may need, at that six hour post dose lab, they may need IV fluids, or they may need Kayexalate to reduce the potassium level or sevelamer to reduce the phosphorus. So you need to plan for those interventions based on what those post dose lab draws show.

Once you get through the five week dose escalation, the other issue that is a big concern with Venetoclax is neutropenia. We do see a high incidence of grade three to four neutropenia. So you want to be monitoring these patients regularly. And again, we liberally use growth factors support to bring this back up, and dose modification if needed. GI distress is one of the less serious side effects but a commonly reported one, especially early on. Once again, we want to try to manage through the symptoms and only utilize dose modification if absolutely necessary.



Slide 58: CD20-Antibody Side Effects and Management

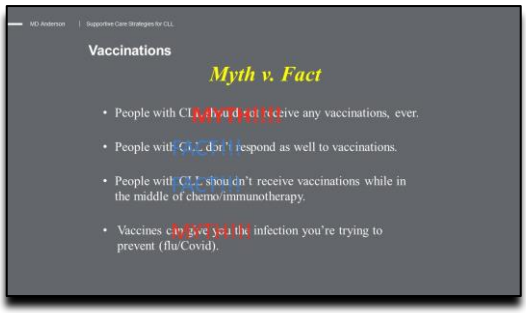
Next, going on to CD20 antibody adverse effects and managements. We do see a fairly high incidence of infusion related reactions with obinutuzumab. So you want to make sure that your infusion center has the protocols in place for this reaction so that they don't have the nurses and the infusion center don't have to page a provider to get instructions on what to do. Those protocols should already be in place. And these should include pharmacologic interventions such as acetaminophen or diphenhydramine and corticosteroids to intervene. And also holding the infusion and then restarting as these infusion related reactions resolve. Pre-medications are particularly important, especially with the first doses and you could typically de-escalate the pre-medications once they get to--usually, once they get to the day eight dose they no longer need as many pre-medications. Tumor lysis can also be an issue particularly with obinutuzumab, so the same precautions apply here, your gas reduction, hydration, and then frequent laboratory monitoring.



Slide 59: CD20-Antibody Side Effects and Management

As mentioned earlier, Hepatitis B virus reactivation is a rare but serious consideration. And so you always want to screen patients for HPV prior to the start of CD20 antibody treatment. And then if they do show a positive result, it's important to consult either infectious disease or hepatology and initiate antiviral therapy. Ideally, you want to get a negative viral load, if at all possible, prior to starting the CD20 antibody treatment. Then there is a black box warning for progressive multifocal leukoencephalopathy, or PML. This is caused by reactivation of the polyoma JC virus. This can be fatal, so that's why it's very

important to be aware of it and to monitor for any potential symptoms. I've never seen it my 15 years. Dr. Wierda, I don't know if you've seen this, but it is something that every provider should be aware of.

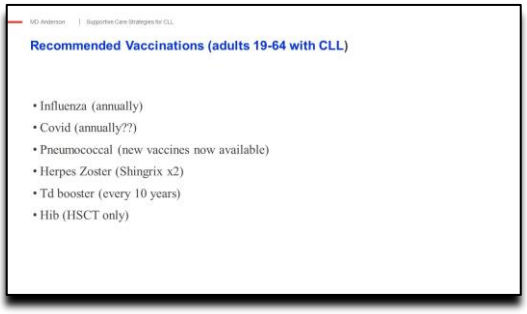


Slide 60: Myth v. Fact

Moving on to vaccinations. Prior to COVID, there was a lot of, not a lot, but there was some controversy with vaccinations and now with thanks to COVID, there's a lot of controversy. So here's some myths versus facts. Number one, people with CLL should not receive any vaccinations ever. That is a myth. Next, people with CLL don't respond as well to vaccinations. That one is a fact. Next, people with CLL should not receive vaccinations while in the middle of chemo or immunotherapy. That is a fact. Again, you don't always have the luxury of timing it outside of of therapy, but if at all possible, you want to time those vaccinations as far apart from treatment doses as possible. And then finally, vaccines can give you the infection that you're trying to prevent such as flu or COVID, and that is a myth.

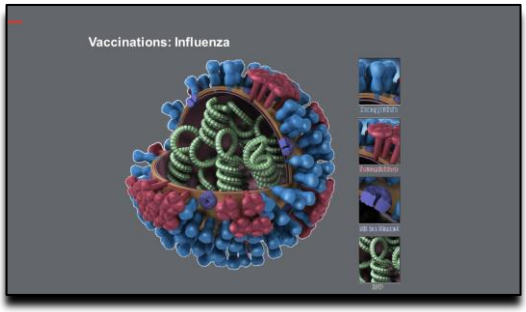
Slide 61: CLL patients should NEVER receive a live/attenuated vaccine

Okay. So CLL patients should never, ever, ever receive a live or attenuated vaccine. These don't come up very often, but the ones to be aware of are MMR, rotavirus, smallpox, varicella, yellow fever, Zostavax is not even available in the United States anymore, and a nasal version of the flu vaccine. So I always just tell patients, look, if you're due for a vaccine, check with us first to see or ask whether it is a live or attenuated vaccine and if it is, be sure to avoid it.



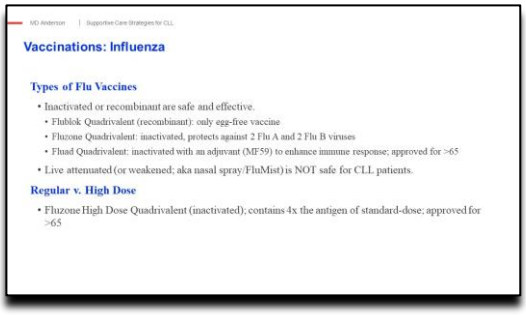
Slide 62: Recommended Vaccinations (adults 19-64 with CLL)

So what are the recommended vaccinations for our adult patients with CLL? We recommend annual flu shots. COVID, we don't know what this will turn into. We're guessing it'll turn into some type of annual vaccination as well. There are new pneumococcal vaccines available. We'll go into those in more detail. Shingrix is the new Zoster vaccination. It's a two dose series. And then a tetanus booster every 10 years. And then the HIV only applies to stem cell transplant patients.



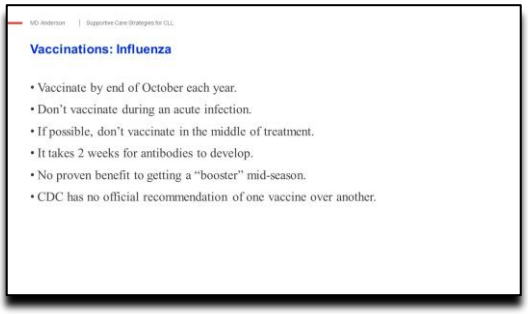
Slide 63: Vaccinations: Influenza

So starting off with the flu vaccine, so the different types of flu vaccines...



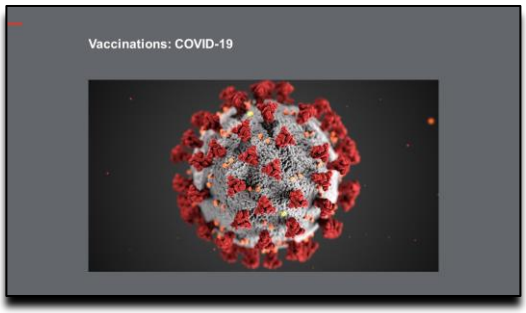
Slide 64: Vaccinations: Influenza

The ones that are safe and effective for our patients are either inactivated or recombinant. The quadrivalent is what you see currently. There's both a recombinant as well as an inactivated form against flu. The recombinant is the only egg free vaccine available. And then there is the high dose version of the inactivated as well, which contains four times the antigen of standard dose. This is technically only approved for patients over the age of 65. So when we try to give it to our immunocompromised patients, we sometimes run into denials from insurance, have to argue our way into that, but ideally, we would like our patients to get the high dose version. The live attenuated, which is the nasal version, is not recommended for our patients.



Slide 65: Vaccinations: Influenza

Basic guidelines for vaccinating against the flu, you want to do this by the end of October. Don't vaccinate during an acute infection. And if at all possible, don't vaccinate in the middle of treatment. It does take about two weeks for antibodies to develop. So if a patient is in the middle of getting their obinutuzumab, you want to time that flu shot to be kind of midway between two of the doses. A lot of physicians like to give a booster midseason. There is no proven benefit to doing this, and this is not part of the CDC recommendations. And of the flu vaccines I just presented, CDC does not make any recommendation of one vaccine over another.

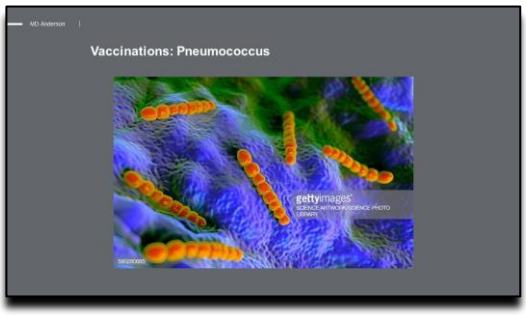


Slide 66: Vaccinations: COVID-19

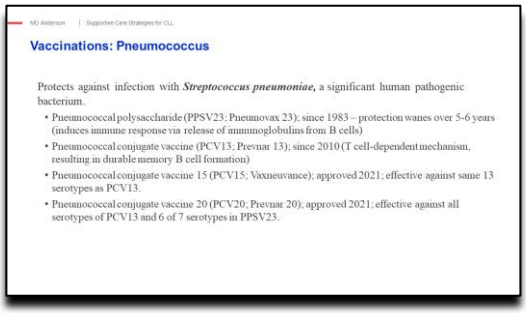
Next, COVID-19. So yes, we are still recommending this for our patients.

Slide 67: COVID-19 vaccination – YES, we are still recommending it for our patients!!!

We are awaiting recommendations moving forward. Everyone should have gotten the bivalent booster. That would be the most recent COVID vaccine available that patients should have had, but this goes through the schedule for the different types of COVID vaccines that are available. I'm not going to--in interest of time, I'm not going to go into all of those. I think most of us are fairly familiar with that. And then what about Evusheld? This is a monoclonal antibody that we were giving to patients as a preventative measure, particularly CLL patients who are on therapy, but because of the evolution of the COVID virus, this is no longer authorized in the United States. So we don't know if they're going to come up with a newer version of this but for now, we are no longer giving it.

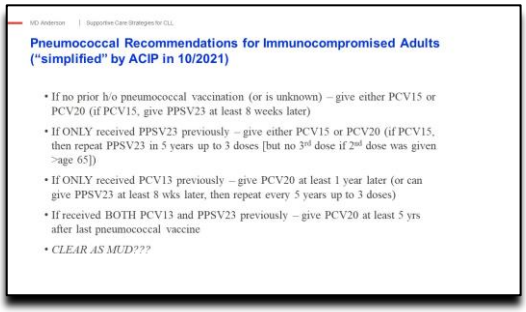


Slide 68: Vaccinations: Pneumococcus
Pneumococcal vaccinations have evolved as well.



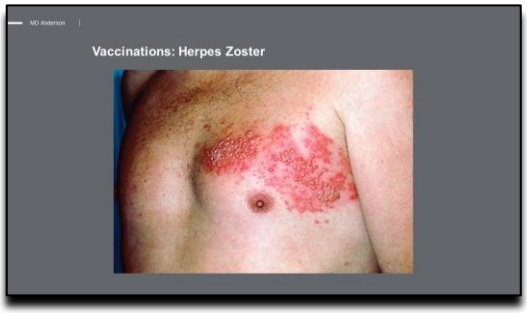
Slide 69: Vaccinations: Pneumococcus
These are the vaccinations that protect against streptococcus pneumonia, which is a very significant pathogen for developing pneumonia. So the top two are the ones that have been traditionally used, the PPSV23, also known as Pneumovax, has been around the longest, and its protection wanes over five to six years because of the way it is designed. And so that's why patients were getting a booster of this vaccination at five years and then as a third dose at five years.

Then we got the Prevnar13 or PCV13. This came around in 2010. It has a different mechanism of action and so it's more durable protection. And we are recommending both of these for our patients. But two years ago, we had two new pneumococcal vaccines approved, the PCV15, which is effective against the same 13 serotypes as a PCV13. So it's basically replacing the Prevnar13. Then also in 2021, the PCV20 or Prevnar20 was approved, and this is a one and done. You get this and it covers everything. So I don't know why you would do the 15 instead of the 20, other than availability. But I attempted to make sense of the recommendations.



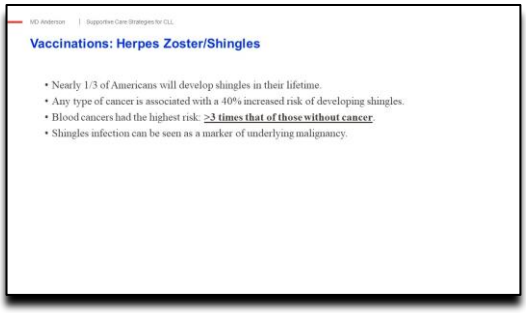
Slide 70: Pneumococcal Recommendations for Immunocompromised Adults ("simplified" by ACIP in 10/2021)
And still, even now, I have to go back and reread the recommendations every time it comes up, because it's a little confusing. But basically, if they have no prior history of any pneumococcal vaccinations, you want to give either of the two new ones.

Again, I don't know why you would get PCV15 if you have access to PCV20. But if you do get 15, then know that you want to give the PPSV23 at least eight weeks later. If they've only received the 23 previously, then again, you can give either one of the two new ones, but if you give the 15 then you got to repeat the 23. If they've only received 13 previously, then you can give the 20 at least one year later, or the 23 eight weeks later and then repeat every five years. If they receive both of the earlier versions, then wait five years and give the 20. I hope that is clear.

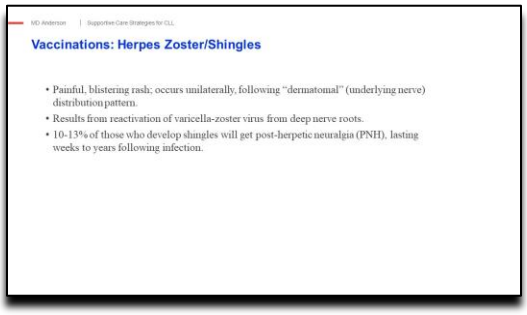


Slide 71: Vaccinations: Herpes Zoster [Image]
Okay. Next, we're gonna talk about herpes zoster. This is what it looks like. It is nasty. You don't want it.

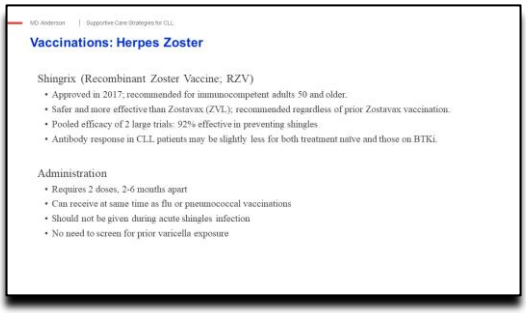
Slide 72: Vaccinations: Herpes Zoster [Image]
You especially don't want it in your eye. This can lead to blindness. So this is a very important vaccination to educate our patients on because they are at increased risk.



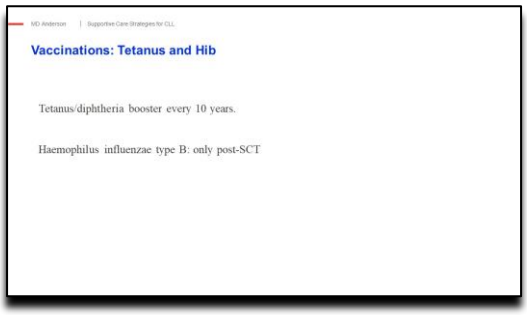
Slide 73: Vaccinations: Herpes Zoster/Shingles
So nearly 1/3 of all Americans will develop shingles in their lifetime. And of course, our patients ever at our a particularly higher risk of developing this. Blood cancers have the higher risk, and sometimes shingles can be the one thing that leads to them eventually being diagnosed with an underlying malignancy such as CLL.



Slide 74: Vaccinations: Herpes Zoster/Shingles
We all know what it looks like and what it can cause. Let's talk about the vaccinations. The Shingrix is the new one.

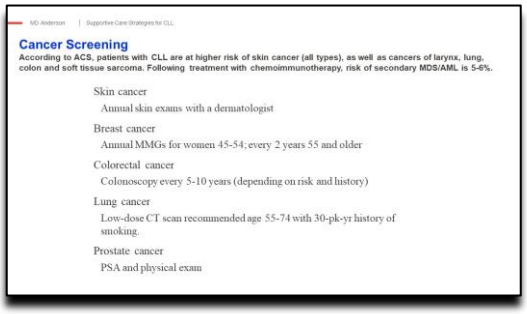


Slide 75: Vaccinations: Herpes Zoster
This is recombinant, which means it is safe. It was approved in 2017. And it's not only safer but is also significantly more effective than the previous Zostavax, which is no longer available in the United States. The pulled efficacy of two large trials showed a 92% efficacy in preventing shingles, we don't yet have those types of long term studies in CLL patients, so the protection may be slightly less. And this is why we are still recommending giving patients antiviral protection while they're on treatment. It's a two dose series to the six months apart, and they can receive it at the same time as other vaccinations, shouldn't be given during an acute shingles infection, and you do not need to screen for prior varicella infection prior to giving us this vaccine.



Slide 76: Vaccinations: Tetanus and Hib
Tetanus every 10 years. Haemophilus Influenza type B is only post-transplant.

Slide 77: Cancer Screening
Cancer screening, getting to the last part of my presentation.



Slide 78: Cancer Screening
According to the American Cancer Society, patients with CLL are at higher risk of all types of skin cancer, as well as cancers of the Larix lung, colon and soft tissue sarcoma. And then we have the risk of secondary MDS or AML, which is higher in the era of chemo immunotherapy at about 5% to 6%. So the screening for these cancers, the recommendations are no different for CLL patients than they are for the rest of the population, it's just making sure patients are actually compliant with these recommendations. So at every visit, we're reminding them about getting their skin cancer exam, getting their mammogram and doing their colonoscopy. That's just part of our kind of routine visit with our patients.

Okay. I wanted to leave time enough for questions, so I will now turn it back over to Lauren.

Lauren Berger
Thank you, Jill. And thank you and thank you to Dr. Wierda also for both of your very informative and comprehensive presentations.

Slide 79: Free LLS Resources for Healthcare Providers
I'm now pleased to share free resources for you from The Leukemia & Lymphoma Society, many of which offer free CME and CE credit. Please visit our continuing education webpage, lls.org/ce for webinars on topics such as blood cancer, 101, CAR T-cell therapy, hematopoietic stem cell transplantation, elevating equity and caring for patients and several other upcoming programs. You can also download our healthcare professional fact sheets, including one on COVID-19 which talks also about the some of the vaccines. Our fact sheets are on a variety of topics.

I also encourage you to listen to our podcast channel, treating blood cancers, where health care providers discuss treatment, side effect management and supporting their patients.

Slide 80: Free LLS Resources for Patients

Leukemia & Lymphoma Society information specialists are highly trained oncology nurses and social workers who provide accurate, up to date, disease and treatment information as well as support, including financial. Patients can contact them directly, or you can help them access the information resource center by completing a referral form.

Information specialists can also help you access or order free copies of booklets to give to your patients. Our critical to trial nurse navigators in the clinical trial support center are registered nurses and nurse navigators with expertise in blood cancers. They work one-on-one with patients via telephone to provide user friendly information, help provide an appropriate clinical trial and personally assist them through the clinical trial process. They also provide information for the patient to bring to their health care provider. This is really a unique service from LLS.

Also, refer your patients for a one-on-one nutrition consultation with one of our registered dieticians through LLS's pro point nutrition services. Consultations are by phone. They're available for patients of all cancer types and all ages and are available in many languages using our interpretation service. I hope you will consider all of these specialists as an extension of your health care team.

Slide 81: Free LLS Resources for Patients

LLS offers blood cancer disease specific information and resources to patients and caregivers, including telephone and web education programs, videos, podcasts and booklets. The LLS Health Manager is an app that enables patients and caregivers to use their phone to manage daily health by tracking side effects, medication, questions to ask their healthcare team and set reminders to take medications. I encourage you to stay up to date on LLS's financial assistance programs, as well as additional support resources using the link on this slide.

Slide 82: Free LLS Resources for Your Patients

And here are examples of booklets that you can order from LLS at no charge. Patients, once again, can access them from the website or you can provide them. Booklets on CLL provide information to help patients better understand disease, treatment, second cancer risks and the need for follow up care. All of our materials are available in English and Spanish. And if you have questions on any of the LLS resources, please contact an information specialist.

It is now time for the question-and-answer portion of the program.

Slide 83: Q&A

Lauren Berger

So first question, what is the best way to diagnosed relapse? Can you diagnose it without marrow by just looking at the labs? And if so, what labs should be looked at and how frequently?

William Wierda

So I'll take that one. So there are standard criteria that we use for relapse, disease and progressive disease. Those require evaluation by physical exam. We can also detect enlarged lymph

nodes by CAT scan, but I don't usually do serial CAT scans to detect recurrent disease unless patients have some symptoms that would warrant doing a CAT scan. Blood counts are important, so you can detect recurrent disease with a rising white count, particularly a rising absolute lymphocyte count.

And I should probably also point out that we don't start retreatments unless patients have an indication for treatment as they do in the frontline setting as well. So those are CLL related symptoms that we want to go away, like fatigue or night sweats or a low hemoglobin less than 11 or a low platelet count of less than 100,000 to initiate retreatment.

Lauren Berger
Okay. Thank you. And the next question. Can you please provide additional insights into the treatment strategies being developed to overcome BTK resistance?

William Wierda
Yeah. So BTK resistance we do see, that is reflected in our rising white count or enlarging lymph nodes while patients are on a BTK inhibitor. That's clinical progression or clinical resistance. In that setting, it's not uncommon for patients to have a mutation in BTK or PLCgamma2 and there is a drug currently, as I mentioned in my talk, pirtobrutinib, which is a reversible inhibitor of BTK. It does not bind to the same location. It binds to a different location of BTK than the irreversible inhibitors. It is currently approved for patients with mantle cell disease, and hopefully it will be available for our patients with CLL in the near future, but pirtobrutinib is one strategy for patients who are resistant to BTK inhibitor. Venetoclax can be used also in that setting, and then there are a number of agents that we're studying in clinical trials, CAR T-cell therapy, MS553 of the protein kinase C beta inhibitor, etc.

Lauren Berger
Okay. Thank you. The next question, and I know you talked a little bit about this, so you answered the first part of it. The question was, what do you see as the role of BTK inhibitors? And the second part, though, is how do you manage coagulopathy in patients with CLL?

William Wierda
So I guess the question I would have is, what does the person who's asking the question meaning by coagulopathy? So I would probably need a little bit more detail about what they're referring to. For the BTK inhibitors, it is contra indicated to use them in combination with warfarin. So we don't give BTK inhibitors with warfarin. We can use an oral anticoagulant, what are referred to as the DOACs with BTK inhibitor, but I don't use the BTK inhibitor plus a DOAC plus aspirin. I don't like having patients on all three agents. That is a risk for bleeding events. So I'll only have them on two. Usually, I'll stop the aspirin in that setting.

Lauren Berger
Okay. Thank you. And we'll take one more question. How do you use MRD status for treatment decisions in CLL?

William Wierda
We don't use it for treatment decisions unless it's being done on a clinical trial. MRD status correlates with outcomes, progression free survival and overall outcomes from a treatment if you do testing for MRD at the end of a fixed duration treatment, but there are no clinical trials that clearly demonstrate how to use MRD in terms of making treatment decisions. So it's only prognostic at end of fixed duration treatment. We are engaging in a number of clinical trials that should help clarify how it's useful in directing therapy, but we need data in order to make those recommendations, which we don't have yet.

Slide 84: Thank you

Lauren Berger
Okay. Thank you. And thank you for all the questions. Our webinar has come to an end. I want to thank Dr. Wierda and Ms. Miller for your continued dedication to patients and healthcare professionals and thank you to all of you for participating. We hope the information presented will be useful in your work with patients. We look forward to your participation on future LLS education programs. Have a great day.

William Wierda
Thank you, Lauren.