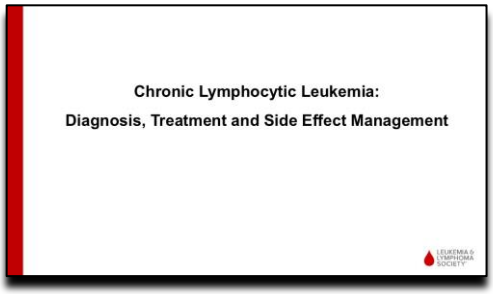
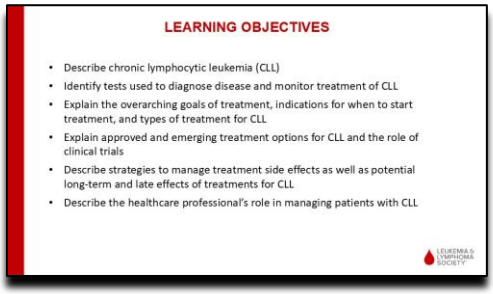


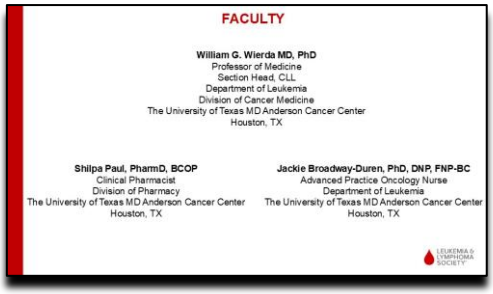
Slide 1: Chronic Lymphocytic Leukemia (CLL): Diagnosis, Treatment and Side Effect Management

Hello everyone. On behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us for this continuing education program on Chronic Lymphocytic Leukemia: Diagnosis, Treatment, and Side Effect Management.



Slide 2: Learning Objectives

The learning objectives for this program are listed on this slide.



Slide 3: Faculty

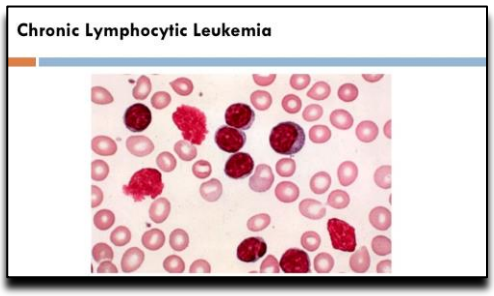
We're fortunate to have as our presenters, Dr. William Wierda, a leading expert in CLL, & his colleagues, Dr. Shilpa Paul, a clinical pharmacy specialist and Dr. Jackie Broadway-Duren, a nurse practitioner. Dr. Wierda is Professor of Medicine, Section Head, CLL, Department of Leukemia, Division of Cancer Medicine, at the University of Texas MD Anderson Cancer Center, in Houston, Texas

Dr. Shilpa Paul is a Clinical Pharmacy Specialist, Leukemia, in the Division of Pharmacy, at The University of Texas MD Anderson Cancer Center, in Houston, Texas.

Dr. Jackie Broadway-Duren, is a nurse practitioner, in the Department of Leukemia, at The University of Texas MD Anderson Cancer Center, in Houston, Texas.

We appreciate their dedication & their commitment to caring for patients living w/blood cancer. I am now privileged to turn the program over to them.

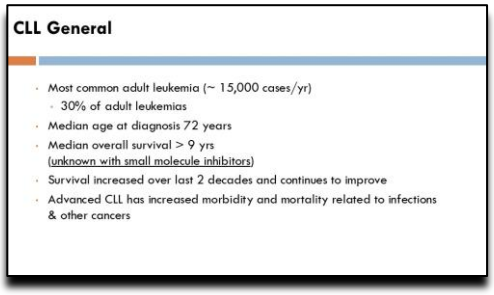
William Wierda, MD, PhD: All right, thank you. Over the next 20, 25 minutes or so, I'm going to review chronic lymphocytic leukemia. This will be sort of a general discussion and start with a diagnosis, and I'm going to talk predominantly about treatment and treatment outcomes; and Dr. Paul is going to talk about specific treatment agents and side effects, and toxicities as well.



Slide 4: Chronic Lymphocytic Leukemia

So, some general comments about chronic lymphocytic leukemia. This is typically diagnosed on routine blood counts, and the peripheral blood smear is reviewed with a microscope; and this is what is typically seen. Those larger cells that have a dark nucleus are chronic lymphocytic leukemia cells. They're relatively uniform in shape and size, and they look like typical and pretty normal lymphocytes. And we don't know that it's actually a malignancy until we do some additional testing, such as flow cytometry.

Those two cells to the left that look like they're smashed cells are referred to as “smudge cells”. That's an artifact of staining; and, really, the only disease that we see smudge cells in is CLL. So, if you see the words smudge cell, then you should be thinking chronic lymphocytic leukemia.

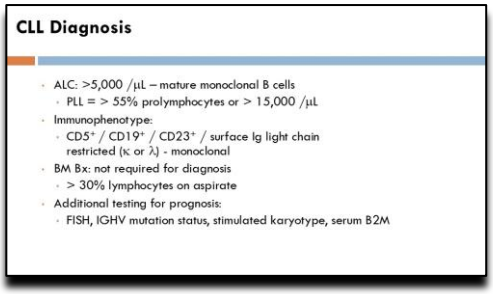


Slide 5: CLL General

It's the most common type of leukemia in the US. It's more common in the aging population. The median age at diagnosis is 72 years. We'll talk a little bit about indications for treatment. Most patients don't need treatment at initial diagnosis, but are monitored and observed. So, the median age at first treatment is typically several years later. So, median age at initial treatment would be 75 or older.

We have made remarkable advances in treatments, as you'll hear about. We've moved away from chemotherapy. Most of the data that is published and reported on in terms of overall survival relates to outcomes in the era of chemotherapy-based treatment. And so, those numbers are old and outdated, and our survival numbers are much better than what you'll see in textbooks these days, because they haven't had a chance to update those numbers with our new targeted therapy.

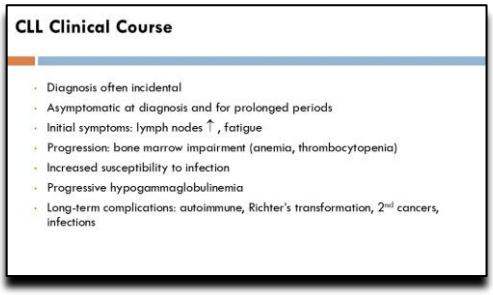
There are specific issues with patients who have this disease, and, also, because of the age of the population, there are some limitations in terms of tolerability and toxicities that we see, even with the newer agents. But that was particularly true with chemotherapy. We'll talk about that.



Slide 6: CLL Diagnosis

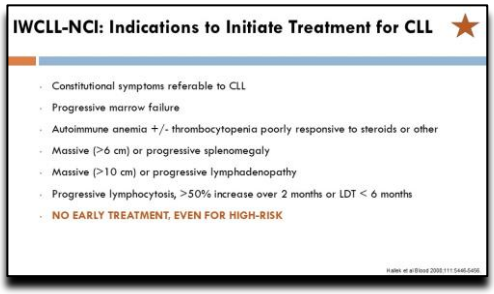
These are the diagnostic criteria, as I mentioned. Typically, the scenario is: an individual goes in for routine blood count. They notice that there's an elevated white blood cell count and, in particular, an elevated lymphocyte count. That blood can be sent for special testing, referred to as flow cytometry; and, with that flow cytometry, the proteins on the surface of the cell can be characterized and identified; and there's a particular signature of those proteins on the surface of cells that identify CLL cells. They either have a kappa or lambda light chain on them, and they express CD5, which is usually found on T-cells; CD19, which is typically found on B-cells; and CD23, which is typically found on activated B-cells. So, it's that constellation of markers that identify these cells, the CLL cells, and make the diagnosis.

That's important, because there are other diseases that can look like CLL under the microscope, but are not CLL, and one of the ways that we can potentially distinguish from those other diseases is what's called the immunophenotype, or the markers that are on the cells. You don't need a bone marrow to make the diagnosis. The diagnosis can be made on the blood sample, and there are additional tests that can be done that correlate with prognosis for patients and can be useful for treatment; and I'll talk a little bit more about that in a minute.



Slide 7: CLL Clinical Course

As these are some of the clinical characteristics, most of the time the diagnosis is made incidentally. Patients don't initially need treatment, and they can be observed. They do have an increased risk for infection. They have an increased risk for second cancers, and so those are features that are very important; particularly these days, when our patients are living very long lives because we need to make sure that they have good health and maintain their health and identify other cancers early so that they can be appropriately managed.

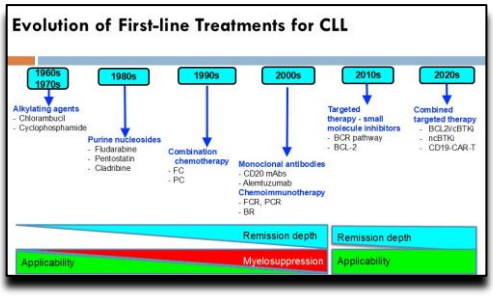


Slide 8: IWCLL-NCI: Indications to Initiate Treatment for CLL

Now, there are trials that have been done that have looked at outcomes for patients if patients are treated at diagnosis versus watch and wait until they have indications for treatment or evidence of active disease. Those trials did not show any benefit for early treatment, and so we monitor and observe

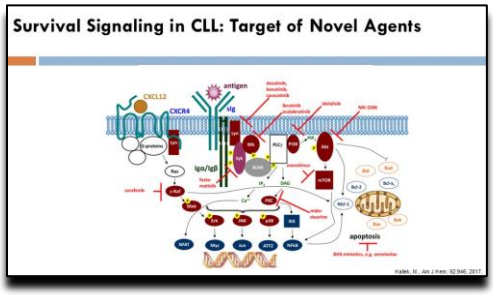
patients until they have an indication for treatment. And this slide shows you the indications for treatment. They can be symptom related; so fatigue, night sweats, unintentional weight loss; and those need to be significant. Or, they can be related to the blood counts, particularly the hemoglobin and the platelet count.

The white blood cell count is not usually used as a trigger for treatment, but the hemoglobin is, and it's a hemoglobin of—consistent hemoglobin of— < 10 to 11 or a platelet count that's consistently less than 100,000. So, we typically, in patients who are on watch and wait, will monitor and observe; and when patients come in for their follow-up, we discuss and talk about what symptoms they're having, and we review their blood counts to determine whether or not there is an indication for treatment. Early treatment is not indicated, even for patients who have a high-risk feature; and we'll talk about what those high-risk features are in a minute.



Slide 9: Evolution of First-Line Treatments for CLL

Now, this is a cartoon that sort of shows the evolution of treatment, and treatment has evolved significantly over several decades, moving from chemoimmunotherapy to our current era of targeted therapy. And we'll talk predominantly about the targeted therapy; and, really, chemoimmunotherapy, chemotherapy is obsolete these days. And they, there are not really any situations that I make a recommendation for chemoimmunotherapy.

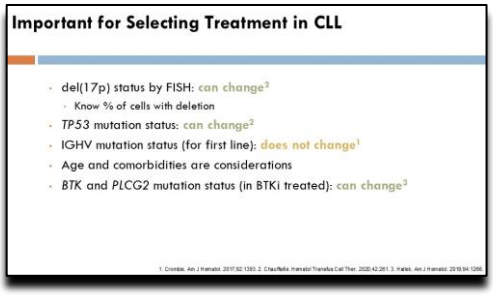


Slide 10: Survival Signaling in CLL: Target of Novel Agents

Targeted therapy refers to agents that specifically bind to proteins and block proteins, and there are sort of two categories of proteins that have been targeted in this strategy. One is members of the B-cell receptor signaling pathway, and, particularly, BTK or Bruton's tyrosine kinase is the target for those agents. Also, PI3 kinase has been targeted, and those proteins being targeting in the sense that small molecules bind to these proteins and block their function. And they have kinase activity, so the small molecule inhibitors will inhibit that kinase activity.

The other sort of category of proteins that have been targeted is the B-cell, BCL-2 family of proteins and, in particular, BCL-2, which is an antiapoptotic protein that's overexpressed in CLL. And when you have a small molecule inhibitor that blocks and, binds and blocks activity of BCL-2, it throws the cells into apoptosis and is very active at eliminating the, the

leukemic cells. And venetoclax (Venclexta®) is the model drug in that category, and you'll hear more about that in a minute.

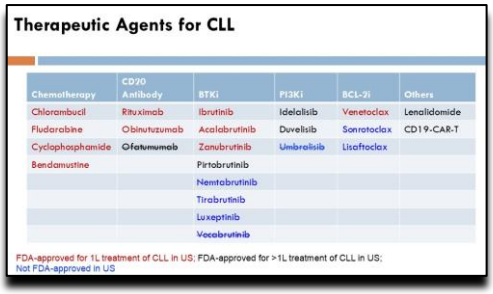


Slide 11: Important for Selecting Treatment in CLL

There are prognostic factors that we evaluate and, in particular, some that are useful in directing treatment. 17p deletion refers to a loss of the short arm of chromosome 17. That is a high-risk feature, and that is identified with a test called FISH, where there's a florescent probe that probes the cells to determine if the short arm of chromosome 17 or 17p is there or not there.

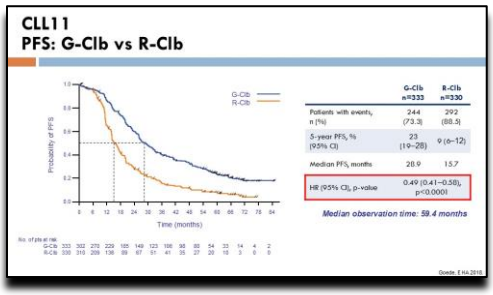
The next is TP53, which is actually the gene that's located on the short arm of 17p. It's a tumor suppressor gene, and if it's mutated or if it's lost, that is unfavorable. So, another test that we do, particularly in patients who are going on treatment, is to sequence TP53 and to determine if it's mutated. Patients who have 17p deletion on FISH, most of them will also have mutation in TP53. Those are very important tests to be done, and they should be done prior to first treatment. And, also, they should be done if patients lose their remission or develop resistance to a treatment and need to change their treatment because you can acquire those, patients can acquire those abnormalities over time.

So, the other important gene or prognostic factor that we can characterize is the immunoglobulin gene, which is present in the CLL cells. And, essentially, this requires sequencing of the immunoglobulin gene—referred to on this slide as IGVHV—and the sequence of that gene is compared to the germline to determine whether or not there's deviation from the germline. If there's more than 2% deviation or more than 2% mutation in that gene, those patients are categorized as having a mutated immunoglobulin gene, which has a more favorable prognosis, a longer time to needing first treatment, improved response to treatment, and improved remission duration. If they have less than 2% deviation, they're considered unmutated, which is a higher risk feature. Age and comorbidities, as you'll hear from Dr. Paul, are very important features. And more recently, with the BTK inhibitors, and I'm sure you'll hear more about this also, we do sequencing of BTK and PLC gamma-2 to determine if those are mutated in patients who have been on a BTK inhibitor, because that can also be helpful in informing and directing therapy.



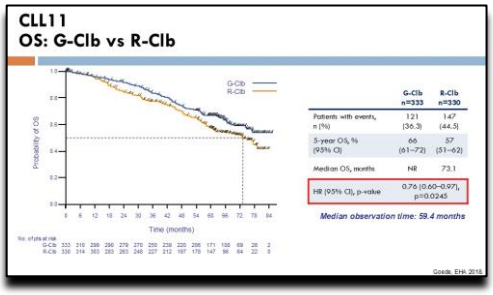
Slide 12: Therapeutic Agents for CLL

A number of agents approved—I'll summarize on this slide—for patients with chronic lymphocytic leukemia, and several drugs still in development for CLL. And you'll hear a lot about several of these.



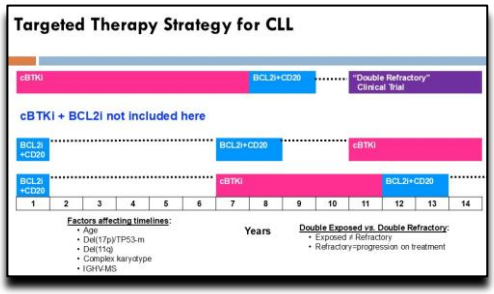
Slide 13: CLL11 PFS: G-Clb vs R-Clb

So, I first wanted to touch on CD20 antibodies, which we've had available for a long time. Particularly, rituximab (Rituxan®) has been available for a couple decades, and trials that have addressed efficacy of CD20 antibodies in patients with CLL. We have had three available, one of which was removed from the market for CLL. That's ofatumumab (Arzerra®). We still have obinutuzumab (Gazyva®) and rituximab (Rituxan®). And this is an early trial that was done to evaluate the efficacy of rituximab (Rituxan®) versus obinutuzumab (Gazyva®) in frontline treatment of patients in combination with chlorambucil (Leukeran®). You can see an improved progression-free survival in the blue curve for patients who receive chlorambucil (Leukeran®) plus obinutuzumab (Gazyva®) or G-CLB, on this slide.



Slide 14: CLL11 OS: G-Clb vs R-Clb

Also, there was an improvement in overall survival for patients who received obinutuzumab (Gazyva®). So, if we talk about CD20 antibodies in the context of treatment for CLL, my preference is to use obinutuzumab (Gazyva®) or, labeled again in this slide, is G over rituximab (Rituxan®).



Slide 15: Targeted Therapy Strategy for CLL

Now, we have again made significant advances in terms of treatment for patients with CLL. If we talk about first treatment, we generally have two categories of treatment options. The first category is treatment with a BTK inhibitor or Bruton's tyrosine kinase inhibitor. That has been developed as a continuous treatment until progression. Extremely effective at treating the disease, very effective at bringing the level of the disease down, but you don't get good deep remissions with the

BTK inhibitors, even in the frontline setting. And, so, they were developed initially as continuous treatment.

We're just now learning what the median progression-free survival is for single-agent BTK inhibitors, particularly ibrutinib (Imbruvica®), which was the first one developed. And the median progression-free survival in the frontline setting with that drug is nine years. So, patients can have a very long period of disease control and very good outcomes with that strategy, although it does require patients to take medicine every day; and, again, it is continuous treatment until progression.

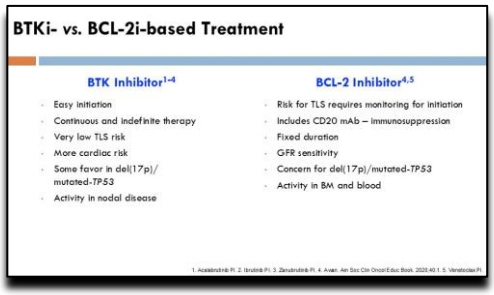
The other strategy that one can take is to use a drug, or combination of drugs, to achieve a very deep remission to get patients off treatment. That can be achieved these days in a nonchemotherapy-based treatment, which is venetoclax (Venclexta®)-based or BCL-2 based. You'll hear some about venetoclax (Venclexta®) plus obinutuzumab (Gazyva®). That was the original trial that was done that supports venetoclax (Venclexta®) in the frontline as an indicated therapy that's given with obinutuzumab (Gazyva®).

With that treatment, which is one year of venetoclax (Venclexta®), the first six months is also given with obinutuzumab (Gazyva®); 75% of patients are MRD-undetectable at the end of the year. And, the overall median progression-free survival in the CLL14 trial is: reported median progression-free survival of six years. I'll show you those data and a little bit about those patients who are at higher risk for shorter progression-free survival. But that's a very, very good outcome; much better than we would see with chemoimmunotherapy for patients with a nonchemotherapy-based treatment.

Venetoclax (Venclexta®) is oral. The BTK inhibitors are also oral. The CD20 antibodies, obinutuzumab (Gazyva®) and rituximab (Rituxan®), need to be given intravenously. But, this slide sort of illustrates something that's important and that we need to think about when we talk to our patients and we present patients with treatment options. And that is, do you want to go on a maintenance-type treatment, which is in pink? If and when you develop resistance to that, you can switch over to an alternative strategy. The BCL-2 or venetoclax (Venclexta®)-based strategy is one option. Now, we have another option with pirtobrutinib (Jaypirca®). In contrast, do you want to take an approach — and there are some other challenges with venetoclax (Venclexta®) that I'm sure we'll talk about — but, do you want to take an approach where you can get a year of treatment to get a good, deep remission and get off treatment and have an average time off treatment of at least five to six to even seven years? And, then, the opportunity or option to retreat with that same treatment to again achieve a remission and be off treatment?

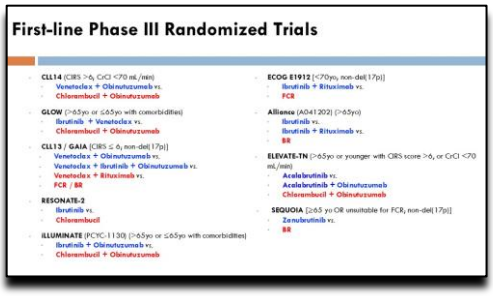
And then, if you ultimately develop resistance to venetoclax (Venclexta®)-based therapy, you can switch to a maintenance; and that's what's shown there in the second and the third row. But this sequencing and strategy, I think, is very important. My opinion is that, if

you commit a patient to a BTK inhibitor-based therapy, you're basically committing them to lifelong therapy. They're going to be on treatment for the remainder of their life. In contrast, if you commit to a BCL-2 inhibitor-based therapy or venetoclax (Venclexta®), then they do have the opportunity to be in a good, deep remission and off treatment. There are shorter remissions as you'll see associated with some features, the high-risk features in particular, and I'll show you those curves.



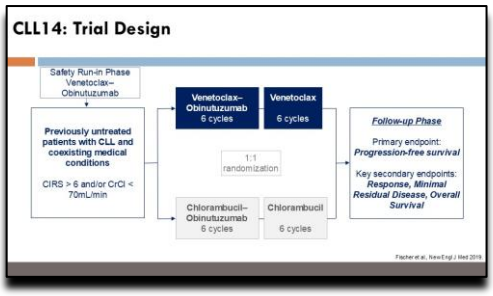
Slide 16: BTKi- vs. BCL-2i-based Treatment

I think Dr. Paul is going to talk about this in contrast to the BTK inhibitor-based therapy in terms of sort of the operational or logistical aspects versus the BCL-2 inhibitor. So, I'll leave that for Dr. Paul to review.



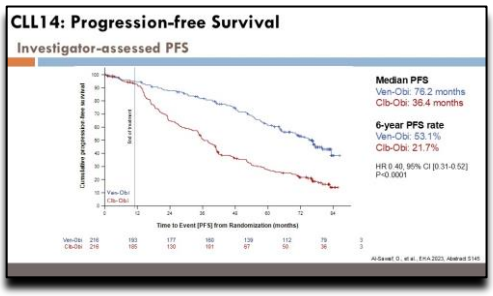
Slide 17: First-line Phase III Randomized Trials

There have been several trials, randomized, Phase III, frontline trials – those are summarized here – that have evaluated targeted therapy, either BTK inhibitor-based therapy or BCL-2 inhibitor-based therapy versus chemoimmunotherapy. All those trials were positive, showing an improved progression-free survival for the targeted therapy over chemoimmunotherapy. And the targeted therapy arms are shown in blue here. The chemoimmunotherapy arms are shown in red. So, a significant amount of data that supports use of targeted therapy over chemoimmunotherapy. Some of those trials have shown even improved overall survival.



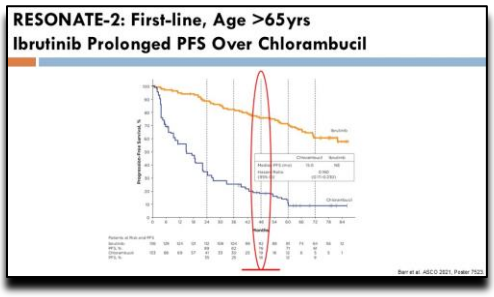
Slide 18: CLL14: Trial Design

The CLL14 trial was a frontline trial with venetoclax-obinutuzumab (Venclexta®-Gazyva®). Those patients who were randomized to receive either venetoclax (Venclexta®)-based therapy or chlorambucil (Leukeran®)-based therapy improved.



Slide 19: CLL14: Progression-Free Survival

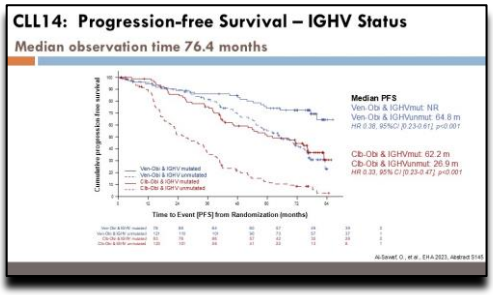
Progression-free survival in blue for venetoclax (Venclexta®)-based therapy with a median progression-free survival of six years overall.



Slide 20: RESONATE-2: First-line, Age >65yrs Ibrutinib (Imbruvica®) Prolonged PFS Over Chlorambucil (Leukeran®)

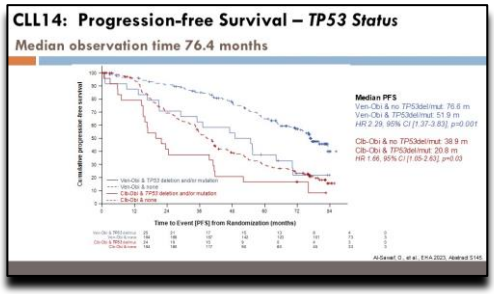
You can identify patients at higher risk for shorter progression-free survival, which I'll show you in a minute.

This fits alongside that data from the RESONATE-2 trial, which is frontline ibrutinib (Imbruvica®), and shows you the progression-free survival in this slide at four years with ibrutinib (Imbruvica®), which was similar to what was reported early on with venetoclax (Venclexta®)-based therapy; the main difference here being different drugs and this is continuous treatment, whereas with the venetoclax (Venclexta®)-based therapy, it was one year on treatment.



Slide 21: CLL14: Progression-free Survival – IGHV Status

Shorter progression-free survival with both treatments but, in particular, paying attention to the blue curves associated with patients who have an unmutated immunoglobulin gene, which is that dashed blue line.

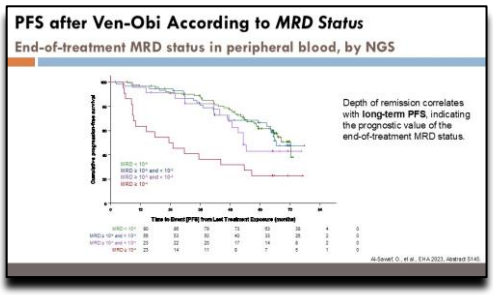


Slide 22: CLL14: Progression-free Survival – TP53 Status

Shorter progression-free survival, and the median for the unmutated cases was five years. And, we don't have a median for patients who have a mutated immunoglobulin gene.

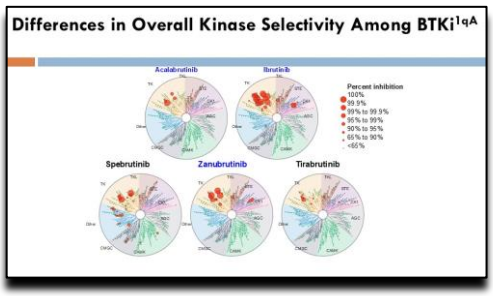
The median progression-free survival for patients who have a 17p deletion or mutated TP53 is shown here in the solid blue curve, and that's shorter at a median of four years. So, you can have three plus years off treatment in remission with 17p deletion, mutated TP53, but they do

have a shorter progression-free survival. And many of us feel that we don't like patients being off treatment who have a 17p-mutated TP53, so that would be a situation perhaps where my preference would be to have patients on a BTK inhibitor as first-line therapy. Everyone else, I like fixed-duration remission and off treatment.



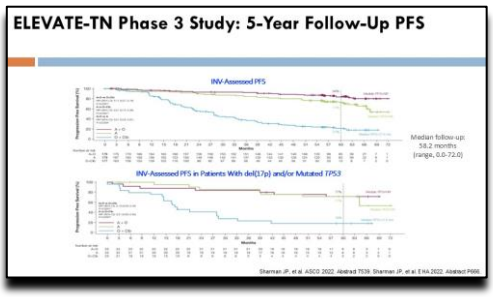
Slide 23: PFS after Ven-Obi According to MRD Status

MRD is also important, and undetectable MRD status is associated with longer progression-free survival, particularly for fixed-duration treatment, like venetoclax (Venclexta®)-based treatment. It's not meaningful in BTK inhibitor-based therapy, but, clearly, it correlates with progression-free survival with fixed-duration venetoclax (Venclexta®)-based therapy and chemoimmunotherapy.



Slide 24: Differences in Overall Kinase Selectivity Among BTKi[1qA]

I'm going to leave the toxicity discussion to Dr. Paul and show you a little bit of data in terms of the BTK inhibitor.

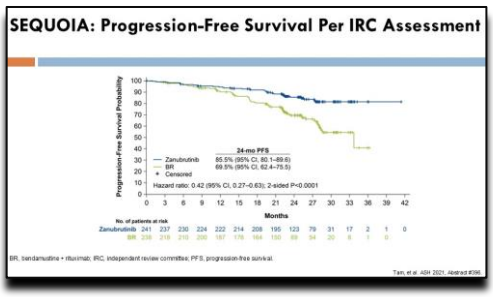


Slide 25: ELEVATE-TN Phase 3 Study: 5-Year Follow-Up PFS

So, I focused first on BCL-2 inhibitor. This is the ELEVATE-TN data. This is a frontline trial with acalabrutinib (Calquence®), which is a second-generation BTK inhibitor. And this was a three-arm trial, two of which had acalabrutinib (Calquence®) comparing chemoimmunotherapy. In this case, it was chlorambucil-obinutuzumab (Leukeran®/Gazyva®). Both acalabrutinib (Calquence®) arms had improved progression-free survival compared to chemoimmunotherapy. One acalabrutinib (Calquence®) arm was the monotherapy, which is in green, and the magenta curve is acalabrutinib (Calquence®) plus a CD20 antibody.

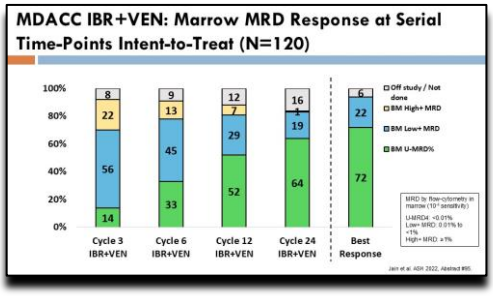
So, you can see on this slide, an improved outcome for patients who have, who receive acalabrutinib (Calquence®) plus CD20 antibody. If you look at the group overall, if you look at the graph below that, that's the 17p-deleted patients; and, a couple things to point out. You don't see the difference between those two acalabrutinib (Calquence®) arms. They're, essentially, superimposed. But you see great outcomes with patients who have 17p

deletion-mutated TP53 with acalabrutinib (Calquence®)-based treatment: 71% progression free at five years.



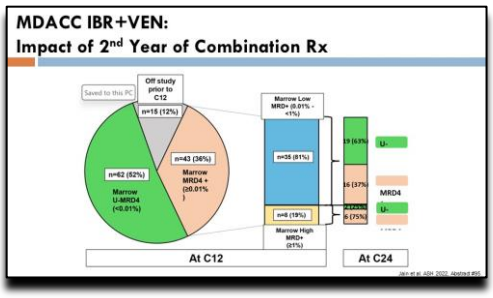
Slide 26: SEQUOIA: Progression-Free Survival Per IRC Assessment

The SEQUOIA trial evaluated zanubrutinib (Brukinsa®), and you can see improved progression-free survival in the dark blue was zanubrutinib (Brukinsa®) versus chemoimmunotherapy. In this case, it was bendamustine-rituximab (Bendeka®-Rituxan®).



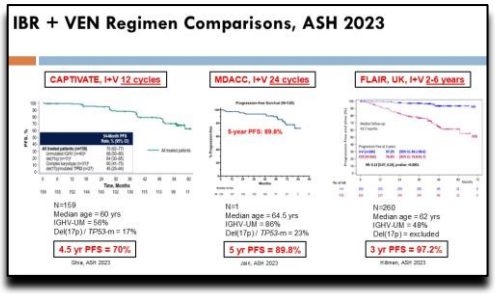
Slide 27: MDACC IBR+VEN: Marrow MRD Response at Serial Time-Points Intent-to-Treat (N=120)

We have done work looking at combinations; combination of BTK plus BCL-2, and then also triplets. BTK, BCL-2, and CD20 antibody. This is more complicated data, and I'm just going to give you a high overview of it. In the green portion of these bars, that is the undetectable MRD rate; and you can see in the bone marrow, significant proportion of patients achieving an undetectable MRD state with combined ibrutinib-venetoclax (Imbruvica®-Venclexta®) in this early trial that we did.



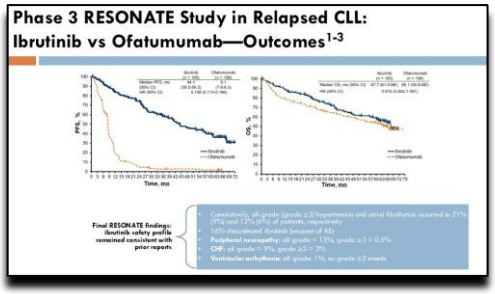
Slide 28: MDACC IBR+VEN: Impact of 2nd Year of Combination Rx

And these patients received two to three years of ibrutinib (Imbruvica®) plus venetoclax (Venclexta®). The important point in this slide is that, between the end of year one and the end of year two, about half of the patients who were MRD-positive at the end of year one converted to MD, MRD-undetectable at the end of year two.



Slide 29: IBR + VEN Regimen Comparisons, ASH 2023

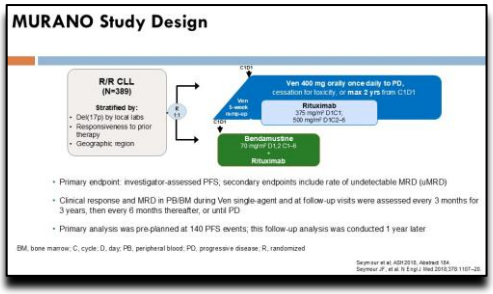
There have been other trials that have looked at fixed-duration, one year of treatment only of ibrutinib-venetoclax (Imbruvica®-Venclexta®), and that is the CAPTIVATE study and the GLOW study. And my opinion is that there is data that supports adjusting the duration of treatment with this regimen where patients who are MRD-positive may benefit with additional treatment: two years, and even three years. The FLAIR study evaluated up to six years of ibrutinib-venetoclax (Imbruvica®-Venclexta®) versus chemoimmunotherapy, and this put side by side the progression-free survival curves for the CAPTIVATE. Our study, which was 24 cycles; the CAPTIVATE study, which was 12; and then the FLAIR study. And you can see a trend of improved outcomes with the additional treatment.



Slide 30: Phase 3 RESONATE Study in Relapsed CLL: Ibrutinib (Imbruvica®) vs Ofatumumab (Arzerra®)—Outcomes[1-3]

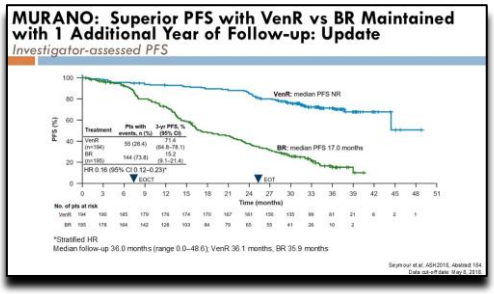
Just to touch on treatment for relapsed disease; and, it's a bit complicated, because the data that we have available for treatment of relapsed disease has been in patients who had chemotherapy before. So, there really isn't much data for patients who never had any chemotherapy and only had targeted therapy.

But we have seen exceptionally good outcomes with treatment for patients who were previously treated with either BTK inhibitor-based therapy, and that's what the RESONATE trial looked at. Those are the blue curves for progression-free survival on the left and overall survival on the right for previously treated patients who received continuous ibrutinib (Imbruvica®)-based therapy.



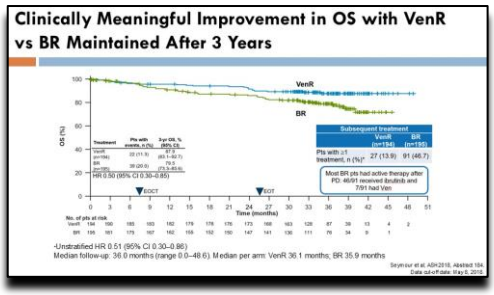
Slide 31: MURANO Study Design

There is also data looking at venetoclax (Venclexta®) in the relapsed setting. That is the MURANO study. In this study, venetoclax (Venclexta®) was combined with rituximab (Rituxan®).



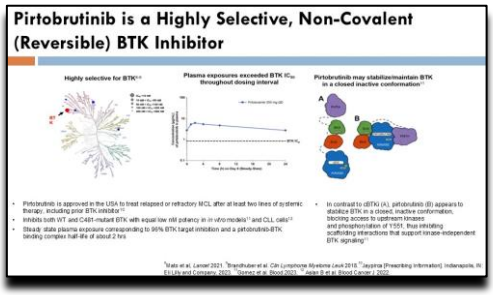
Slide 32: MURANO: Superior PFS with VenR vs BR Maintained with 1 Additional Year of Follow-up: Update

And compared to chemoimmunotherapy, and the report was that there was improved progression-free survival in the light blue curve with venetoclax-rituximab (Venclexta®-Rituxan®) compared to chemoimmunotherapy, which is in the green curve.



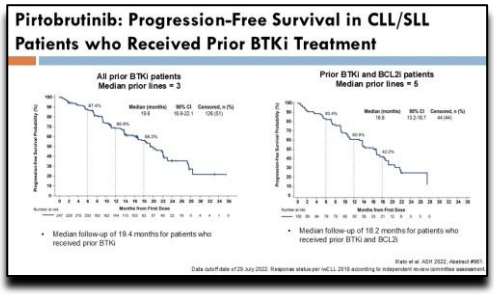
Slide 33: Clinically Meaningful Improvement in OS with VenR vs BR Maintained After 3 Years

And, there was improvement in overall survival with targeted therapy over chemoimmunotherapy, even in the relapsed setting.



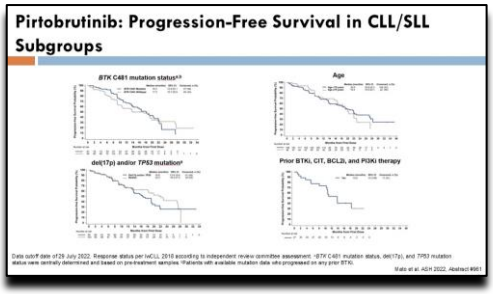
Slide 34: Pirtobrutinib (Jaypirca®) is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

Now, ibrutinib (Imbruvica®), acalabrutinib (Calquence®), and zanubrutinib (Brukinsa®) are all covalent BTK inhibitors. They bind to BTK covalently and irreversibly block the kinase activity. We had worked on a drug called pirtobrutinib (Jaypirca®), which is a noncovalent inhibitor. It binds to BTK but not covalently, and it binds to a different location than those covalent drugs.



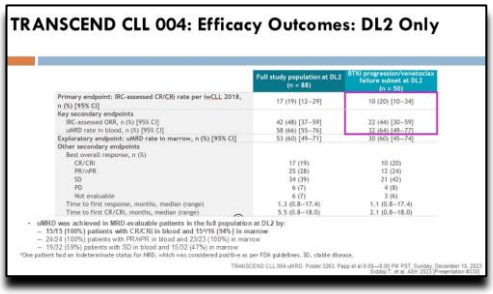
Slide 35: Pirtobrutinib (Jaypirca®): Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

It has a very good toxicity profile and has activity, including in patients who've had a prior covalent BTK inhibitor and/or also venetoclax (Venclexta®)-based therapy. So, this is data from the, what's called the BRUIN study showing progression-free survival in patients who've had prior BTK and BCL-2 inhibitor-based therapy.



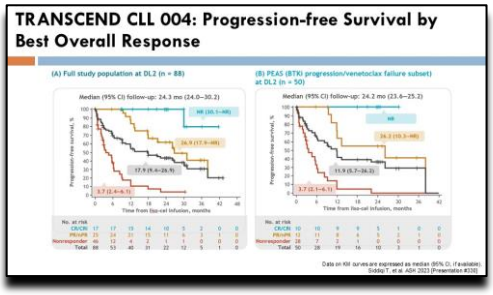
Slide 36: Pirtobrutinib (Jaypirca®): Progression-Free Survival in CLL/SLL Subgroups

And, also, activity in patients who have the cysteine 481 mutation, which is associated with resistance to the covalent BTK inhibitors.



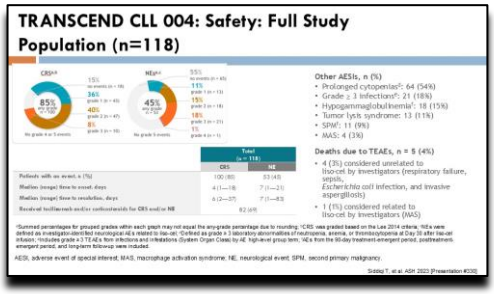
Slide 37: TRANSCEND CLL 004: Efficacy Outcomes: DL2 Only

And then, finally, the TRANSCEND study evaluated CD19 CAR T for patients with CLL in the relapsed setting. And there was certainly activity in treating those patients, with a complete remission rate of about 20%. Overall response rate was about 40%/45%.



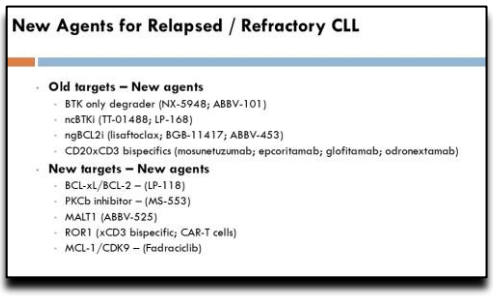
Slide 38: TRANSCEND CLL 004: Progression-free Survival by Best Overall Response

And particularly in patients who were refractory to BTK and BCL-2 inhibitor-based therapy. And those remissions were durable in terms of progression-free survival and overall survival for these patients.



Slide 39: TRANSCEND CLL 004: Safety: Full Study Population (n = 118)

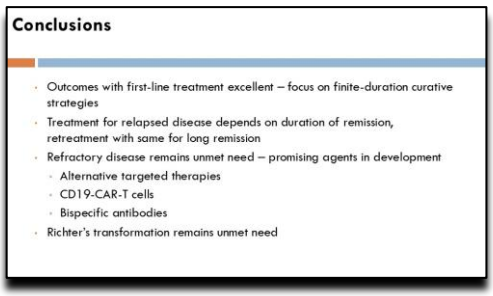
And there was a reasonable toxicity profile in CLL, both with regard to CRS — or cytokine release syndrome — and neurotoxicity. So, this treatment was recently approved for patients with CLL who were referred to as double refractory: BTK and BCL-2 refractory.



Slide 40: New Agents for Relapsed/Refractory CLL

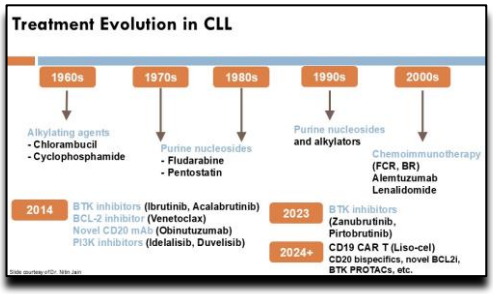
And then, this is my second to last slide, which summarizes the newer agents that are currently under clinical trial, and there are a lot of them. There are BTK inhibitors, noncovalent BTK inhibitors, new next-generation BCL-2 inhibitors, bispecific antibodies, and cell therapy. And, so, there's a lot of activity in this space and opportunity. Our patients are

doing exceptionally well, but there are patients who develop resistance, and I think some of these agents may also be helpful ultimately in developing curative treatments for our patients with CLL.



Slide 41: Conclusions
These are my conclusions.

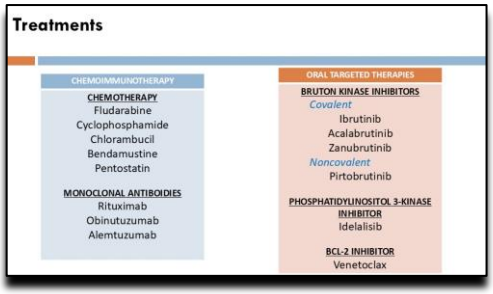
Slide 42: Thank You!
And thank you for your attention.



Slide 43: Treatment Evolution in CLL
Shilpa Paul, PharmD, BCOP: Thank you, Dr. Wierda, for that excellent presentation. I'm going to be focusing more on the drugs and the drug toxicities. As you probably have heard from Dr. Wierda that there are some therapies like the BTK inhibitors that can potentially be taken lifelong; and then there are some more fixed-duration therapies like venetoclax (Venclexta®), obinutuzumab (Gazyva®), or even venetoclax-rituximab (Venclexta®-Rituxan®).

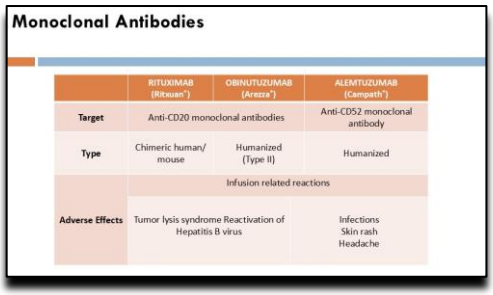
But, a lot of these therapies, the patients are going to be on them for a long duration, at least a year. And, so, it's really important, even as pharmacists, that we make sure that we are minimizing the adverse effects of these drugs and allowing patients to have a good quality of life, especially if they are on these BTK inhibitors long term.

Treatment has significantly evolved in CLL, as you can see here on the slide. We've gone away from cytotoxic chemotherapies to more of these oral targeted agents.



Slide 44: Treatments

And here, you can see the different classes of drugs. So, we have the chemoimmunotherapies. We'll focus more on the monoclonal antibodies. As you may know with chemotherapy in general, they can be very cytotoxic, so they will just generally be cytopenias, myelosuppression, GI side effects, and so on. But with monoclonal antibodies, we focus on very unique adverse effects. And, as Dr. Wierda went over all the data with the BTK inhibitors, we have covalent and the noncovalent pirtobrutinib (Jaypirca®); and we won't really focus on PI3 kinase inhibitors like the idelalisib (Zydelig®) and the duvelisib (Copiktra®)**.** But I will focus on venetoclax (Venclexta®), as that is readily being utilized in the treatment of CLL in combination with the monoclonal antibodies.



Slide 45: Monoclonal Antibodies

We have two of the monoclonal antibodies, obinutuzumab (Gazyva®) and rituximab (Rituxan®). There's also alemtuzumab (Campath®), which I won't focus on. We are not utilizing this therapy, at least in the frontline or even second-line therapy. So, the target of the rituximab-obinutuzumab (Rituxan®-Gazyva®) is really that they're both anti-CD20 monoclonal antibodies.

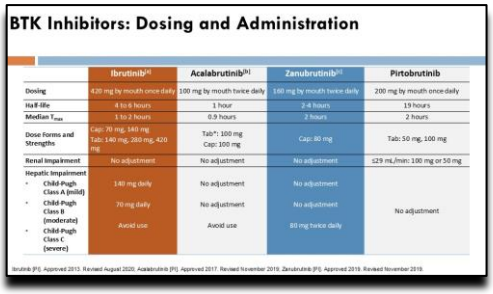
Now comparing to rituximab (Rituxan®), obinutuzumab (Gazyva®) has a lower complement-dependent cytotoxicity, whereas rituximab (Rituxan®) has a stronger complement-dependent cytotoxicity. But obinutuzumab (Gazyva®) actually has higher antibody-dependent cellular toxicity and antibody-dependent phagocytosis, and direct cell death. So, when we give obinutuzumab (Gazyva®) to our patient, you will see like a rapid decline in their white blood cell count. A bit stronger, if I can use that term, of an anti-CD20 monoclonal antibody than rituximab (Rituxan®), and we kind of saw that also in the outcomes that obinutuzumab (Gazyva®) had better favorable outcomes and overall survival than rituximab (Rituxan®).

The things that we need to look out for are infusion-related reactions, so we do premedicate our patient with antipyretic, it could be acetaminophen. And if the patients do have reactions we do add steroids or Benadryl® (Diphenhydramine). In some institutions, that's already built into their treatment plan, where all patients at the beginning get acetaminophen (Tylenol®), Benadryl® (Diphenhydramine), and steroids. So, it may depend on what practice you have.

And then, there's also tumor lysis syndrome, which, as I told you and alluded to, obinutuzumab (Gazyva®) can significantly reduce count. You see that at the very

beginning of the therapy in the cycle. So, the first cycle, usually if the patient has high-risk disease, a lot of tumor burden, we tend to admit them in the hospital. We will cut the dose, the first dose 100 milligrams and then 900 milligrams, split dosing over the two days. And then, after the patient has had that dose, then they can potentially get the rest of the dose as outpatient.

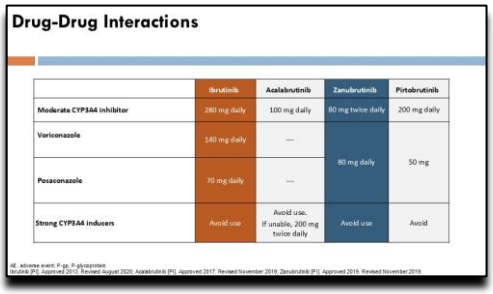
There's also a risk of reactivation of hepatitis B, so it's very important to have that as a baseline to make sure your patients don't have hepatitis B. If they do, then usually we call our ID or we will start entecavir (Baraclude®). It's not a complete contraindication for utilizing these two monoclonal antibodies.



Slide 46: BTK Inhibitors: Dosing and Administration

Moving onto BTK inhibitors, this is the dosing and administration. I'm not going to read this all to you guys, but you can kind of see that acalabrutinib (Calquence®) is one drug that is dosed twice daily. Zanubrutinib (Brukinsa®) is dosed twice daily, but it can be given as a, as a daily drug as well. And, then, you will have to be careful with some renal impairment and hepatic impairment. Renal impairment with pirtobrutinib (Jaypirca®), if the patient was already getting 200 milligrams, and their creatinine clearance is less than 29, then you can do 100. If they were already on 100, then you can reduce it down to 50 milligrams. And then there's some hepatic impairment dose reductions there as well.

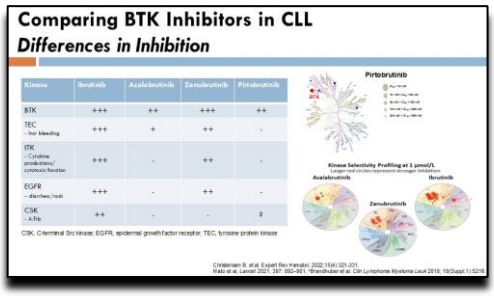
As far as the dosage formulation, as I mentioned, they are just oral. One thing I did want to point out too is: acalabrutinib (Calquence®) no longer has the capsules. They're just tablets, because the capsules did have an interaction with acid suppressing medications, and you were not allowed to have the patient on those drugs concomitantly. But that no longer is a problem with acalabrutinib (Calquence®) with the tablet formulation. And, they've phased out of the capsules.



Slide 47: Drug-Drug Interactions

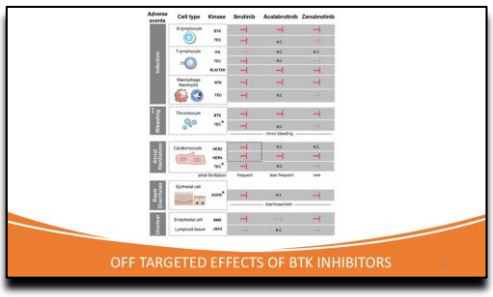
The other thing that we need to really monitor for are drug-drug interactions with these agents. I have listed, here, some agents that we may run into, because BTK inhibitors do have a risk for opportunistic infections — particularly the first generation, like ibrutinib (Imbruvica®) —, and we will kind of hit on that just a little bit.

There may be a possibility that a patient, if they have *Aspergillus* pneumonia or an *Aspergillus* fungal infection, that you might need to use one of these azoles. And, if they need to use it for a longer duration of time, you may need to dose-reduce these agents accordingly. And then we also need to worry about strong inducers or moderate inducers, because it will reduce the serum level of these drugs, whereas the inhibitors will increase the level of the BTK inhibitor; and that can potentially lead to toxicity. We will discuss in a bit.



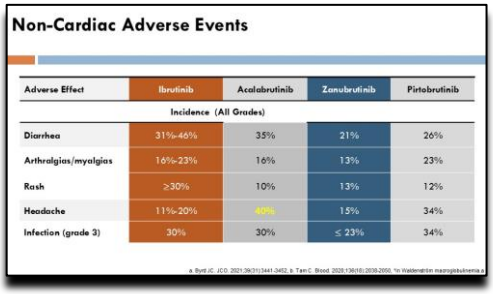
Slide 48: Comparing BTK Inhibitors in CLL *Differences in Inhibition*

Looking at the different BTK inhibitors, you kind of saw a Kinomap that Dr. Wierda had flashed on one of the presenter slides; and, basically, that kind of shows the on-target and off-targeted effects. As we progress through the generations, from the first, second generation and third generation, you get less off-targeted effects with these agents; and, as you can see with ibrutinib (Imbruvica®), there's particular kinases that lead to certain toxicities — like the TEC which increases bleeding risk, the ITK which increases cytokine production, cytokine function, and dysregulation. With EGFR, you are dealing with more diarrhea and potentially rash, and then CSK, along with TEC, can lead to issues with atrial fibrillation; and this is just alluding to ibrutinib (Imbruvica®) kind of having more of these off-targeted effects. And as you move on, you will see less off-targeted effects.



Slide 49: Off-Targeted Effects of BTK Inhibitors

And this is just another slide to kind of present that. The last generation, pirtobrutinib (Jaypirca®) is not on here; but as you can see, ibrutinib (Imbruvica®), acalabrutinib (Calquence®), and zanubrutinib (Brukinsa®), and the different types of kinases and what infections or toxicities they lead to.



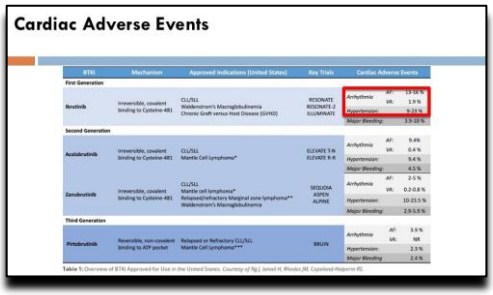
Slide 50: Non-Cardiac Adverse Events

Focusing more on the non-cardiac adverse events that I mentioned, there is kinase inhibition of EGFR; and that can lead to diarrhea and rash. And we can see that a bit more with ibrutinib (Imbruvica®). Diarrhea can occur early on, within the first six months; but usually it ends up being very low grade, Grade 1 to 2. But if the patients do need something, we can treat them with some antidiarrheals.

With acalabrutinib (Calquence®), we see more headaches. And, then, with zanubrutinib (Brukinsa®), we're seeing less of these toxicities in terms of the arthralgia/myalgias, which can really impact the patient's quality of life. As we were mentioning, these BTK inhibitors need to be taken long term. So, some of these arthralgia/myalgias, if we cannot support them through potentially giving them magnesium or quinine/tonic water, if it's really impacting their activities of daily living, we may have to interrupt the BTK inhibitor or we potentially might have to dose-reduce the BTK inhibitor. In clinical practice, we have seen that sometimes dose-reducing can help the patients continue on their therapy. And there is data that, Dr. Wierda can probably speak to as well where we don't necessarily have to give ibrutinib (Imbruvica®) at its highest dose, that there is efficacy also with the lower dosing. But now we have a lot of these other agents to choose from. So, we look at the toxicity profile, and we select the BTK inhibitor that would be the most appropriate for our patient.

The patients that are already on ibrutinib (Imbruvica®) and they're not experiencing toxicity or if they were and they were dose-reduced, we're not pulling the ibrutinib (Imbruvica®) off and stopping it just to switch the therapy to a new agent. We're going to continue the patients on the ibrutinib (Imbruvica®). But, for the patients that are starting new, we do want to look at all of these adverse effect profiles and select which would be appropriate for the patient.

And, as I mentioned, there is a risk for infection with these agents as well, particularly PJP and *Aspergillus.* It's not mandated that you have to give these patients prophylaxis right at the beginning, but if the patient is higher risk; so, say somebody that was heavily pretreated, or patients that have longer-term myelosuppression, depending on their risk or if they're using a lot of steroids, they have other concomitant infections that puts them at risk, those are the patients you may want to consider monitoring carefully or potentially putting them on PJP prophylaxis.



Slide 51: Cardiac Adverse Events

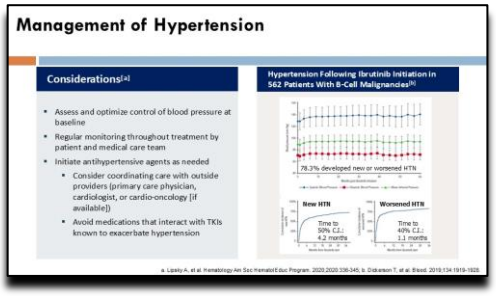
Now, cardiac events are some of the scarier events in clinical practice because we're talking about atrial fibrillation, bleeding. And so, with these agents, the first-generation ibrutinib (Imbruvica®) has the highest risk of arrhythmias. That's atrial fibrillation or ventricular arrhythmias as well as hypertension, whereas the second and third generation will have less.

Now, the mechanism of action for arrhythmias really involves these off-targeted effects like the TEC proteins and the AKT; so, AKT inhibition actually increases sodium current, and

this will prolong the cardiac action potential, which increases the vulnerability of early and delay after depolarization.

Ibrutinib (Imbruvica®) has additional mechanism of actions in which it causes cardiomyocyte dysfunction. But, essentially, these off-targeted effects are leading to potential atrial fibrillation in our patients, and we'll talk about how to manage those. And, then, the other thing is hypertension, which we see more with ibrutinib (Imbruvica®) than the other agents. The mechanism of action is not fully elucidated, but it's been related to, potentially, nitric oxide inhibition, vasoconstriction, and, potentially, fibrosis. So, overall, the incidence, as I mentioned, is higher with a first generation than later generation, and we will also talk about how to manage hypertension.

And the other adverse effect that we have to monitor our patients for is the major bleeding. Most of the bleeding, potentially, is like petechiae. It will be Grade 1 or 2. But major bleeding is greater than 3 or higher. You can see here they all have a risk, these risks and these percentages are really based off of the clinical trials. But all of them can have a small risk for major bleeding due to platelet dysfunction.

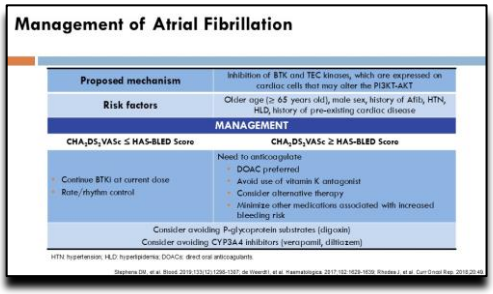


Slide 52: Management of Hypertension

For management of hypertension, you really want to assess and optimize the patient, control their blood pressure, because, as you can see on the slide here, there are patients that can develop new hypertension within a median of about four months. And those that already had hypertension can actually have worsening of their hypertension while on ibrutinib (Imbruvica®).

It's really important to manage and make sure you have the best control of their hypertension if you are going to start the first-line therapy with ibrutinib (Imbruvica®), and then you would want to regularly monitor them throughout the treatment. Involve the cardiology team if necessary.

What's really important, also, is to avoid certain medications that can have interactions that I mentioned; CYP3A4 inhibitors, inducers is really important. And there are certain agents, like verapamil (Calan®) or diltiazem (Cardizem®) that can have interactions. So, working with your cardiology team and having good blood pressure control and monitoring the patient over time is very important. And, if that cannot be managed in patients on ibrutinib (Imbruvica®), you may want to think about switching the patient to another BTK inhibitor.



Slide 53: Management of Atrial Fibrillation

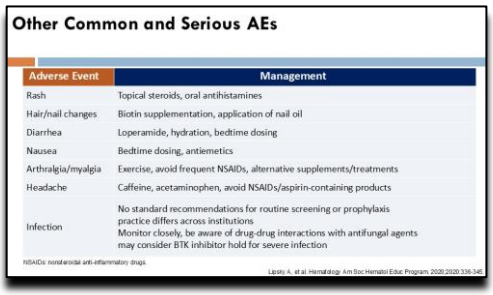
Management of atrial fibrillation — this is very important. In clinical practice, it is a very clinically significant adverse effect that can lead to, potentially, mortality, if it's not caught and treated right away. I kind of already alluded to the proposed mechanism through the TEC and BTK kinases and the AKT. There have been several studies that have looked at certain risk factors. So, older age, history of already having atrial fibrillation, having other cardiac conditions, hypertension, hyperlipidemia. Even males, they're at higher risk for developing atrial fibrillation.

When patients have atrial fibrillation, they may need to be anticoagulated. And, as I mentioned that patients are at risk for bleeding with these BTK inhibitors, so it's really important to also involve your cardiology team and discuss: what is the risk of bleeding versus adding an anticoagulation onboard for these patients?

So, if we look at the bleeding score versus the CHA_2DS_2-VASc Score, which kind of is, 'okay, what is the risk for patients, clot or stroke?' If the patient's CHA_2DS_2-VASc Score is higher, then you may need to give these patients anticoagulation. And, for our patients, these are older patients, they have several comorbidities, so you want to make sure that their bleeding risk is also low, because you don't want them to fall, hit a head, and have potential bleeding.

So, for our patients, when we look at the benefit versus risk ratio and calculate these scores with the cardiologist, if the patients do need anticoagulation, we sometimes use certain agents like apixaban (Eliquis®). Depending on their renal function, we might start at a lower dose and just carefully monitor these patients.

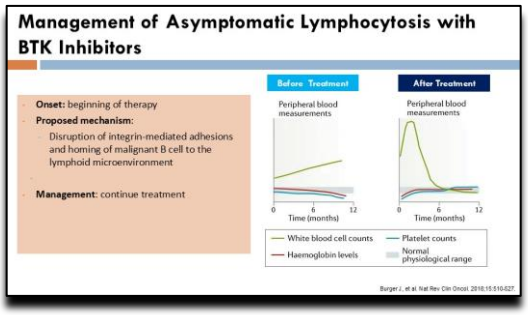
Otherwise, we can use agents for just rate and rhythm control and just continue the BTK inhibitor, again, avoiding agents like verapamil (Calan®), diltiazem (Cardizem®), and so on, and other P-gp substrates like digoxin (Lanoxin®) due to drug-drug interaction.



Slide 54: Other Common and Serious AEs

Going back to: some of the other serious adverse events that we can see with these agents are rash. Usually these are just low grade, Grade 1 or 2. They can occur at any time, but, usually, they happen within the first year. If topical steroids or antihistamines are used, that's fine. Diarrhea happens within the first six months. As time goes on, it should improve. Most of the patients have lower grade, but antidiarrheals, hydration, and potentially taking at bedtime can help patients.

The other thing, arthralgia/myalgias that I have already talked about, we try to avoid NSAIDs; and we tell our patients kind of try light bearing exercises. As I mentioned, magnesium, quinine/tonic water, and then, if the patient needs an NSAID, we usually try to give just a very short course of it, or a short course of steroid can also be given. Headache is something that you see more with acalabrutinib (Calquence®), and you can generally give patients acetaminophen (Tylenol®), caffeine, and that also improves over time as the patient continues the therapy. There should be less occurrences of headache. And then, infection, again, just letting you know that PJP and *Aspergillus* infection, opportunistic infections are more common; and then prophylaxis is really just needed for those patients that are potentially at higher risk.

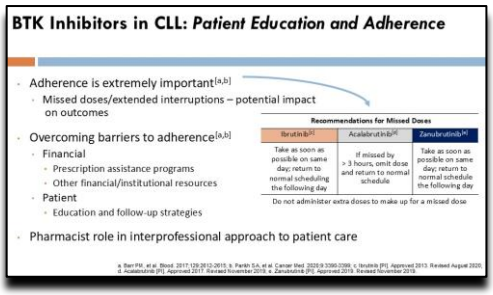


Slide 55: Management of Asymptomatic Lymphocytosis with BTK Inhibitors

The other thing that can happen that's really not an adverse effect, it's how the drug is actually working. So, in one of the slides, Dr. Wierda had that BTK inhibitors really worked well with the lymph nodes. And so, what's essentially happening, at the beginning of your therapy, there's a disruption of integrin-mediated adhesions and homing of malignant B-cells to the lymphoid microenvironment. And, when you start these therapies, it's pushing those CLL cells out into the periphery. So, from the lymph nodes into the blood.

And when you are getting your bloodwork done on a patient, you see these increased lymphocytes there; and you may worry, "Oh, my gosh, the patient is relapsing or the therapy's not working." But actually, it's an indication that this is working because it is pushing those CLL cells out into the periphery.

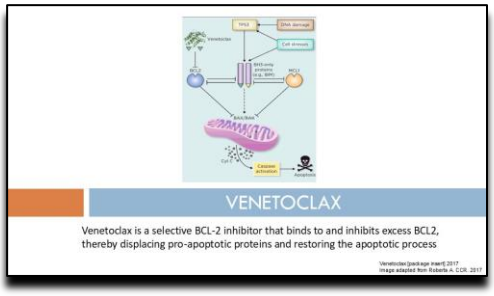
So, after treatment, you can see that bump in the peripheral blood; and that is okay. It's just asymptomatic lymphocytosis that occurs with BTK inhibitors. But, it is something to be monitored.



Slide 56: BTK Inhibitors in CLL: *Patient Education and Adherence*

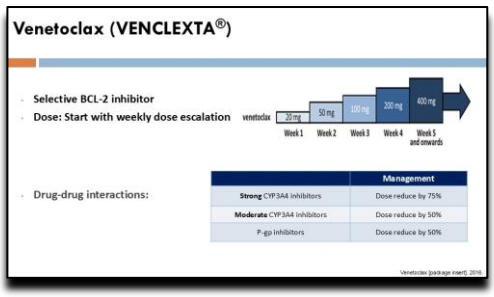
As I mentioned, BTK inhibitor education. Patient education's very important, particularly because these therapies are taken long term, so we need to educate our patients about the potential adverse effects and also be able to mitigate these side effects. So, we need to tell them adherence is also important because, obviously, the drugs are only going to work if they adhere to them and take them properly. So, we will educate them on

this dosing, and then also sometimes there can be barriers with financial burden for these patients, and that's really where LLS and other foundations can come in and even the manufacturers.



Slide 57: Venetoclax (VENCLEXTA®)

Moving onto venetoclax (Venclexta®), which is important oral chemotherapy in CLL.



Slide 58: Venetoclax (VENCLEXTA®)

It is a selective BCL-2 inhibitor that Dr. Wierda already spoke about; and he also spoke about it as in combination with obinutuzumab (Gazyva®) and rituximab (Rituxan®). Venetoclax (Venclexta®) can cause significant tumor lysis, and it can also lead to cytopenias. I've already talked about how obinutuzumab (Gazyva®) can really bring down the counts, and when we combine it with venetoclax (Venclexta®), you can only imagine that it is even stronger in the fact that it can cause significant myelosuppression. So, we have to be very cognizant and careful when giving the patients these combined therapies and monitoring their white counts. In order to decrease the risk for tumor lysis syndrome, I'll show you in the next slide what can be done. But venetoclax (Venclexta®), unlike in AML, is really given in a stepwise fashion.

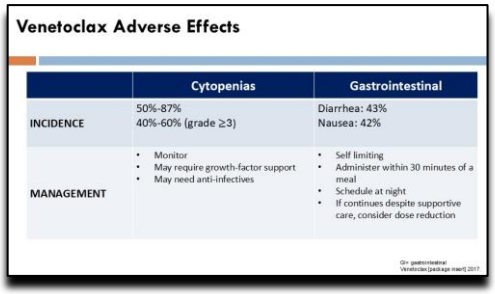
So, the first week, you do 20 milligrams, then 50 and 100 and 200 and 400. So, every week, the patient is stepping up. The nice thing is, when you prescribe venetoclax (Venclexta®), you prescribe it as a starting dosing pack; and it already comes in a dosing pack of telling patients how to take it for the first four weeks. And there are significant drug and drug interactions, just like the BTK inhibitors. So, if you have a strong or moderate inhibitor, you need to adequately dose-reduce the venetoclax (Venclexta®).

Slide 59: Schema

Here is a schema of how we determine if the patient is at low, medium, or high risk for tumor burden. If the patient is at high risk for tumor burden — just like we do for obinutuzumab (Gazyva®). If the patient has a high risk for tumor burden: Any lymph node over greater than or equal to 10 centimeters; or they have

lymph node; but their also absolute lymphocyte count is also high, greater than 25 × 10^9.

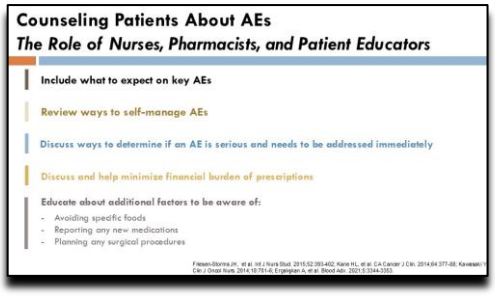
So, those things help us determine whether the patient is high, medium, low risk. The high-risk patients will be admitted for monitoring of their tumor lysis. What we do to help mitigate this is add oral hydration or IV hydration, and, also, allopurinol (Zyloprim®). If the patients need rasburicase (Elitek®), in our case, we do give it to them as well. Once they're out of that period of tumor lysis, then we can potentially give these agents outpatient.



Slide 60: Venetoclax (Venclexta®) Adverse Effects

I've already talked about the tumor lysis. The other things that can happen with venetoclax (Venclexta®) are the cytopenias and the GI side effects. Cytopenias, I've already talked about. We monitor the patients. Some patients may need growth factor support and/or some dose reductions for future cycles. But the good thing in CLL, unlike AML, is that we can give patients growth factor support if they have cytopenias at Grade 3 or higher.

And some patients may need anti-infectives, but mostly the patients tend to get growth factors; and then, usually, their white counts recover, and you don't necessarily need to give them anti-infective therapy in CLL. GI side effects, they're pretty self-limiting, but we do encourage our patients to take a low-fat meal within 30 minutes of taking venetoclax (Venclexta®), or they can schedule it at night. And then, just, if they continue to have the GI side effects, then we just give them some supportive care or potentially dose reduction. Some patients, if they have diarrhea, giving them antidiarrheal helps.



Slide 61: Counseling Patients About AEs: The Role of Nurses, Pharmacists, and Patient Educators

It's very important to, again, involve not only just the pharmacist, but also nurses and anybody that does intake. You need to tell the patients what to expect with these oral therapies. Also, self-management; we do have an oral chemotherapy clinic that is run by pharmacists in conjunction with the physician. So, any time patients get oral therapy, it's prescribed for CLL, our pharmacists are calling them immediately to educate them about the adverse effects, and also to tell them how to take it, and about adherence. And then,x we follow them up regularly for the first year to make sure that we have the best outcomes. Because if the patients are experiencing adverse effects, they may stop taking the drug, and that's not what we want.

So, we have all of these discussions to kind of minimize that, and we also try to help minimize the financial burden with these prescriptions.

When patients are first diagnosed, come in, and say they don't have TP53, I have seen a lot of institutions kind of think about fixed-duration versus just BTK inhibitors. And I will kind of talk about BTK inhibitors and how we select first generation versus the second generation. But how do you go about determining whether you want fixed-duration and a BTK inhibitor for a patient?

Dr. Wierda: So, my preference overall is to have patients in remission, off treatment. That we can do with BCL-2 inhibitor-based therapy. And, so, my preference is for fixed-duration or finite duration venetoclax (Venclexta®)-based therapy to achieve remission over BTK-inhibitor-based maintenance, except for patients with a 17p deletion mutated TP53. So, most of the trials that are being done today — and most of our clinical trials — are looking at fixed-duration treatments and regimens and working towards improving the depth of remission and the proportion of patients in an undetectable MRD remission with combinations of venetoclax (Venclexta®)-based therapy.

So, that is my preference. I think patients, in general, prefer to be off treatment, in remission. One of the challenges with venetoclax (Venclexta®)-based therapy is the tumor lysis and the initiation. Also, patients who have renal insufficiency, it can be a problem and may not be an option if their creatinine clearance is less than 30. So, I, but my preference overall is for fixed-duration treatment.

Dr. Paul: Yeah. And I think I hear that from different practices, as well. If they can do fixed duration, that would be great. And, I think, patient selection, as you mentioned, is really important; not just deletion 17p or TP53, but also, can the patient handle that myelosuppression and cytopenia?

And, and with BTK inhibitors, one thing would be the financial toxicity or burden of it because the BTK inhibitors are taken for a long duration of time. It's kind of like a chronic condition at that point versus something that's fixed-duration; and that is really important for some patients that we take in consideration, particularly if they have high copays.

Obviously, we don't know that information right off the bat when we have the patients diagnosed. But talking about how to select BTK inhibitors, as I had mentioned with first-generation ibrutinib (Imbruvica®) of moving onto the second and third generation, you see less off-targeted effects. And that really becomes important for patients with compliance, because when we only had ibrutinib (Imbruvica®) as the first generation and first-line therapy for BTK inhibitors, we didn't have any other option, so we had to do ibrutinib (Imbruvica®) and we had to do a deal with atrial fibrillation and hypertension.

And there are studies that have looked at ibrutinib (Imbruvica®) compared to acalabrutinib (Calquence®) and zanubrutinib (Brukinsa®). So with the ALPINE study comparing the efficacy of zanubrutinib (Brukinsa®) to ibrutinib (Imbruvica®), we saw that zanubrutinib

(Brukinsa®) had sustained progression-free survival benefits over ibrutinib (Imbruvica®) and higher overall response rate than ibrutinib (Imbruvica®).

But not only just the outcomes — it was also the discontinuation rate. So, zanubrutinib (Brukinsa®) had lower treatment discontinuation rates than ibrutinib (Imbruvica®); ibrutinib (Imbruvica®) was like almost double that of zanubrutinib (Brukinsa®). Discontinuation due to adverse events was 16% in the zanubrutinib (Brukinsa®) group and 23% in the ibrutinib (Imbruvica®) group. And zanubrutinib (Brukinsa®) also had lower cardiac-related adverse effects. Cardiac effects like atrial fibrillation. So, based off of these head-to-head trials, it does tell us that when patients are first diagnosed and we're thinking about a BTK inhibitor, ibrutinib (Imbruvica®) is kind of phasing out as the therapy of choice, where, if you're just doing single-agent BTK inhibitor, we would go with either acalabrutinib (Calquence®) or zanubrutinib (Brukinsa®). I don't know that any head-to-head trial right now, Dr. Wierda, and I don't know if one will be done with acalabrutinib (Calquence®) versus zanubrutinib (Brukinsa®), and it probably will not be done. But, that ibrutinib (Imbruvica®) was kind of the gold standard at that time, so we do have data to kind of look at acalabrutinib (Calquence®) and zanubrutinib (Brukinsa®) and, also, just sequencing of it. Is that important for you because I know there are studies; but sequencing on BTK inhibitors, does that matter in clinical practice, Dr. Wierda?

Dr. Wierda: There's not any data that specifically answers that question, but I do think it probably will end up being important. And, I think, what you're alluding to is for the RET BTK inhibitors, patients who are developing resistance to therapy will typically acquire a C481 mutation, if they're progressing on ibrutinib (Imbruvica®) or acalabrutinib (Calquence®) or zanubrutinib (Brukinsa®). The other mutations that we see are much less frequent.

Whereas, for patients who are on pirtobrutinib (Jaypirca®), they're noncovalent and progressing, we do see other mutations associated with resistance: the 528 and the 474 mutation. We see the C481 go away in patients who had it when they went on pirtobrutinib (Jaypirca®). When they respond, they lose that mutation.

We see resistance with 528 and 474 for the covalent inhibitors. So, I worry about sequencing where we might start pirtobrutinib (Jaypirca®) and they could acquire a resistance mutation that would prevent them from going to getting a good response and durable response with, with covalent BTK inhibitors.

So, anyway, right now pirtobrutinib (Jaypirca®) is relatively restricted in its usage based on the label, so that patients have to have had a prior BTK inhibitor, a covalent BTK inhibitor before they go on pirtobrutinib (Jaypirca®), which I don't think, right now, is a bad situation to be in.

Maybe the other comment I would make is, in terms of the covalent BTK inhibitors, I'm seeing, lately, where insurance providers will limit options to either ibrutinib (Imbruvica®) or zanubrutinib (Brukinsa®), or ibrutinib (Imbruvica®) or acalabrutinib (Calquence®). I think that has a lot to do with, sort of, contractual agreements and the fact that there isn't any data that demonstrates that acalabrutinib (Calquence®) versus zanubrutinib (Brukinsa®), there's a difference in terms of efficacy. Most insurance companies will give you the option of one of the second-generation BTK inhibitors. And, I think, if patients are asking questions and are nervous about limitations in terms of which second generation, that probably isn't a big issue as long as they get access to one or the other.

Dr. Paul: And switching from one therapy to the other, as you just mentioned, it's not like we have data. But, in terms of just treating the patient frontline that hasn't necessarily failed a BTK inhibitor, switching patients due to adverse effects, to acalabrutinib (Calquence®) and zanubrutinib (Brukinsa®), we do in clinical practice still see patients have efficacy with either one of these agents. What you want to make sure before switching, if, say, you see that patients having a lack of response is if they have any of those mutations, where you wouldn't be able to use the acalabrutinib (Calquence®) and zanubrutinib (Brukinsa®) and, then, you would have to use pirtobrutinib (Jaypirca®). So, that is really important in clinical practice that we are assessing when to switch and when it's appropriate to test for those mutations before changing the agent.

And a lot of these agents, we're starting to see, are being combined. So, either, with monoclonal antibody — and you kind of showed ibrutinib (Imbruvica®) plus venetoclax (Venclexta®). Is that changing any of your practice currently, or you're still kind of thinking BTK inhibitors or fixed-duration with venetoclax-obinutuzumab (Venclexta®-Gazyva®) if the patient is newly diagnosed? I mean that data has yet to fully come and have, and have FDA approval. But, where do you see that in changing practice?

Dr. Wierda: The BCL-2 plus BTK?

Dr. Paul: Correct.

Dr. Wierda: Yeah. So I think the data that are emerging suggests that there are some patients who benefit more from that combination. Particularly, patients with an unmutated immunoglobulin gene have a higher undetectable MRD rate than patients who have a mutated immunoglobulin gene.

So, targeted plus BTK plus BCL-2, that situation, my preference is that measurement for patients with an unmutated immunoglobulin gene. I like a CD20 antibody for patients with a mutated immunoglobulin gene, so I'm okay with venetoclax (Venclexta®) plus obinutuzumab (Gazyva®) for patients who have a mutated immunoglobulin gene getting first-line therapy. I think that's probably a better treatment than a BTK plus BCL-2, ibrutinib

(Imbruvica®) plus venetoclax (Venclexta®), for example, because patients with a mutated immunoglobulin gene are having a lower MRD undetectable.

Great. Now, those patients do well anyways because their disease is slower growing. But, if you really want to optimize their response and outcome, you really want them in an undetectable MRD state. And it's probably best to achieve that with venetoclax (Venclexta®) plus obinutuzumab (Gazyva®).

Dr. Paul: And how important is it to achieve MRD-negativity? If a patient comes and says, "Well, this therapy has emerging activity, and we're not seeing that with BTK inhibitors as single agent," we're not going to get that.

Dr. Wierda: Well, there are trials. We're doing a trial looking at fixed-duration BTK inhibitor-based therapy. So, patients get two years of either zanubrutinib (Brukinsa®) plus a CD20 antibody or acalabrutinib (Calquence®) plus a CD20 antibody. So, we're looking at responses and how long patients are off treatment and if they're at risk for developing, acquiring resistance mutations in that setting. And I think others will be doing those types of studies.

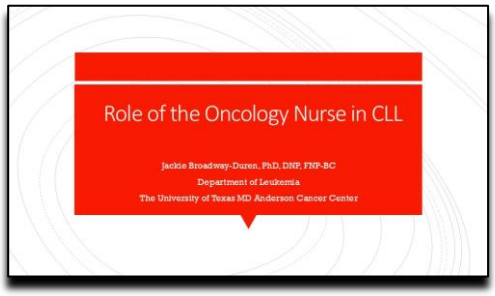
So, fixed-duration in the future may not only apply to venetoclax (Venclexta®)-based therapy, but may apply to BTK inhibitor-based therapy. I think we need data that supports that. For now, if you select a BTK inhibitor-based therapy, you're committing patients to continuous treatment until progression.

Dr. Paul: And how often are you seeing that — patients that are on long-term BTK inhibitors, you're having to switch therapy or dose-reduce because of toxicity?

Dr. Wierda: I would say, probably, if we start with a second-generation BTK inhibitor, switching is less common than if we started with a first-generation. And dose reduction also is less common with the second-generations compared to the first-generation. So, I would say less than 30%, 40% currently, starting with a second-generation BTK inhibitor, for switching or dose modification. So, we covered a lot of material today. We focused on targeted therapy and, as you can see from the data we covered, our outcomes are improving and continuing to improve with our new combinations of targeted therapy. These drugs do have some side effects and toxicities associated with them, but are much better tolerated in our patient population than chemoimmunotherapy, and that really has improved outcomes for our patients.

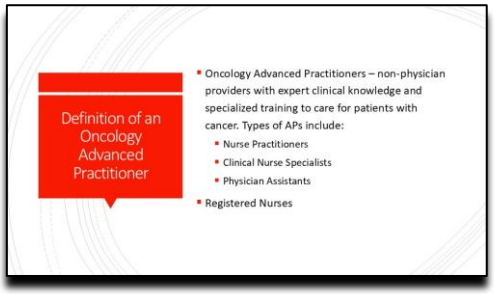
So, I think it's been a great review and discussion of data. Thank you, Dr. Paul, for your time and for your expertise and discussion, and thank our audience for listening and participating.

Dr. Paul: Thank you, Dr. Wierda. I think this was very informative and great discussion.



Slide 62: Role of the Oncology Nurse in CLL

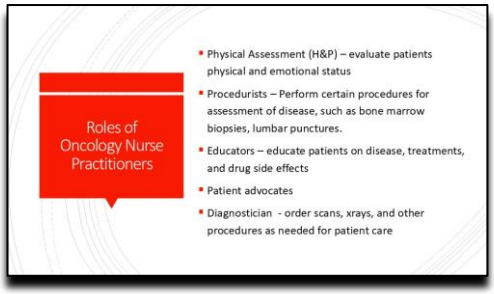
Jackie Broadway-Duren: Hello. My name is Jackie Broadway-Duren, and I will be presenting to you today on the Role of the Oncology Nurse in Chronic Lymphocytic Leukemia, also most commonly known as CLL.



Slide 63: Definition of an Oncology Advanced Practitioner

So, I thought, as we initiate this presentation, I would talk about what is the definition of the various roles that are involved in patient care for CLL. So, there's the oncology nurse, of course, who is the core of the team, which consists of often a physician, advanced practice provider listed below, and a registered nurse.

So what are advanced practice providers? We are non-physician providers with expert clinical knowledge and specialized training in the care of various types of cancer patient, as is the case of CLL patients. These advanced providers would consist of nurse practitioners, clinical nurse specialists, and then see Physician Assistants. However, the focus of this talk will be oncology advanced practice nurses and RNs.



Slide 64: Roles of Oncology Nurse Practitioners

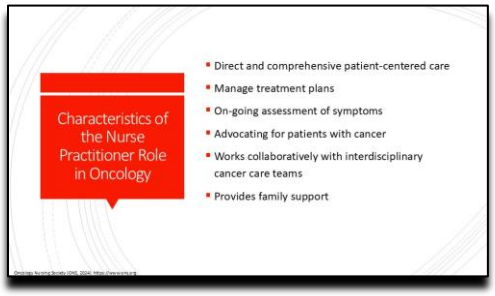
So, what are some of the roles of the oncology nurse practitioner? And, as I discuss these various roles, I will also point out to you where the RN works alongside the advanced oncology nurse. So, both of the roles, at times, will be interchangeable.
So, the first role that we'll talk about is physical assessment, and this is where we evaluate the patient's physical and emotional status. Physical assessment begins upon the patient entering the clinic. Sometimes, physical assessment is not always just hands on. It's looking at the patient, evaluating their moods, evaluating what their physical status is, and all of this at the time that the patient come in starts at the beginning of the visit. Again, this role is interchangeable with RNs and advanced practice nurses.

Then, there are the procedurist roles where, again, the RNs assess with certain procedures, such as assessment of disease states, bone marrow biopsies, and lumbar punctures. Where they are not doing hands-on care, they are actively there at the bedside

with the advanced practice provider as they provide these procedures. Their role in this instance is oftentimes reassuring the patient, helping to position that patient, and, then, giving any premedications of sedation and those type things.

The next, and one of the most important roles, is the educator role. We all educate patients at every aspect of the patient care. From the time that patient enters the room, patient education begins. The patient is educated on the type of disease, the treatments that may be available, possible side effects of those treatments, as well as what all is involved as far as managing the patients' daily regimen and making sure that they're taking the treatments and adhering to the treatment regimens.

And, another one of the most important roles is patient advocates. We, as nurses, advocate from the patients, for the patients from day one. Again, we as nurses, no matter whether it's advanced practice or bedside registered nurses, or research nurses who are generally also RNs, are our patient advocates from day one. We advocate as far as emotional needs. We'll assist the patient in getting housing. We'll assist the patient in understanding the drugs and how they should be taken and all those things. And then again, importantly, we also advocate in bringing that family in because that is a significant part of a successful patient treatment. And lastly, diagnostician, this is more of the advanced practice role — ordering scans, medications, and, again, procedures and whatever's needed in patient care.



Slide 65: Characteristics of the Nurse Practitioner Role in Oncology

So, what is some of the characteristics of the advanced practice nurse? Direct and comprehensive patient-centered care, managing treatment plans while we work together with the physician as a team — which consists generally of the physician, advanced practice provider, and the nurse. We manage treatment plans once they have been determined; and how that treatment plan may affect their patients' daily life and how their work regimen, their family regimen, all these things may fit into making sure that that patient has a successful outcome with their treatment plans.

There is always ongoing assessment of symptoms. When these patients are enrolled on these treatment plans and they've started these drugs, they make pretty frequent visits to the clinic for evaluation; and, whether or not they are physically onsite at the clinic or whether they are on the phone or MyChart or whatever, we are always assessing for symptoms.

The patients themselves often say to us in clinic, "No, I'm not tired today. No, I haven't had night sweats." And, most times, they're being facetious. However, these are questions that

they must answer each time that they come into the clinic. So, the physical assessment, as well as emotional overall assessment of patient symptoms, are always ongoing. We know that specific drugs can cause diarrhea and other GI symptoms. So, of course, when the patient is being treated with those particular drugs that we're going to focus, particularly the nurse, that is the first person that rooms the patient and spends time going over that review of systems with the patient. So, their assessment then clues in the advanced practice nurse practitioner and physician as to things that we need to focus on once we get into the room with the patient for assessment.

Again, nurses are always advocating for patients with cancer; and, sometimes, that may be trying to find somewhere for the patient to stay temporarily when they must be there in the medical center for an extended period of time. Sometimes, it's spiritual care that they may be advocating for. In the event where there are patients who may be having some psychological or emotional distress, the nurse is usually the first one to recognize this and contacts social work and bring them into the environment. We all work collaboratively together as an interdisciplinary team to promote the best possible outcomes for cancer care in our patients.

And we don't leave out the family. As you all know, if you don't take care of the family, then that affects the patient's care and outcome. So, it's very important to include the family in these meetings that we have with the patients each time they come into clinic, unless it is the patient's preference not to include the family. But family support is included as our comprehensive care model.

Slide 66: Symptom Management

As far as symptom management, we all become experts to some degree in symptom management that is caused by certain treatments, such as the BTK inhibitors. Now, all of us nurses, advanced practice nurses, and anyone that cares for these patients over any period of time know that there are some specific symptoms or adverse events that may occur with patients on specific types of drugs.

For example, with the BTK inhibitors, we make it a point to make the patient aware that you can possibly have joint pains; or you may, and most likely will, see bruising; that the patient may have problems with GI symptoms, such as diarrhea and, in some cases, constipation.

So, we know that the best thing for us to do is sit down and discuss these possible adverse events with the patient outside of what the pharmacist and the physician may have already discussed. As in the case of the research RN, they generally spend more time with the patient as far as discussing symptoms; and, early on, the patient is introduced to possible

treatment or management strategies such as, for instance, in the case of diarrhea. We often tell these patients to go ahead and be proactive and maybe get an antidiarrhea medication that you can purchase over the counter and have that handy in the event that they may develop these GI symptoms. There are also other ways of managing things such as joint pains. We try not to encourage a lot of pharmacological intervention where just commonsense things can be suggested to the patient. And again, this is where the RN is very helpful in reassuring the patient that these joint pains that you may feel are likely transient and they may grow from one joint to the next, but it's common that these can occur with this particular type of treatment.

Again, often, there are various strategies for management of adverse drug events. Now, there have been cases where patients reported headaches with certain classes of these inhibitors, so you want to offer them strategies for management of headaches, such as, for example, caffeine. It may be something as drinking a cup of coffee or a cup of tea to help assist with headaches rather than drug intervention in these cases. Again, this is where RNs are invaluable, because they generally have more contact and time with that patient initially and on the backend of starting treatment.

Provide a detailed explanation of treatment drugs and regimen. This lies more likely with the advanced practice nurse practitioner or/and in addition to the registered nurse who is classified as a research nurse, because they are the managers of these protocols and treatment regimens. So, who best to talk to that patient, who best to have more time to engage in explanation of the drugs and what these regimens entail.

It is very important that the patient is fully abreast of not only which drugs in the regimen, what is the time that is involved — the time commitment. These RNs who serve as research nurses are key to that patient maintaining drug compliance. They monitor and count these drugs that are given to the patient as part of a protocol, a research protocol, and they have a very close working relationship with the patient.

Whereas the advanced practice nurse practitioners generally deal with the patient more so on-site when they are in clinic managing any physical symptoms that they may exhibit, talking to the patient, answering emails on MyChart, prescribing things that may be needed to assist the patient as far as their drug treatment. Also, we work very closely with the PharmDs as far as explanation of treatment. The PharmDs have a program where they contact the patient so many days after they've gone on treatment and touch base with them, you know, to make sure that they are staying on task with their drug regimens.

There are times when the patients have to have some type of pharmacological intervention to manage adverse events. Again, this will fall more into the role of the advanced practice nurse to prescribe things, such as for maybe acid reflux or other type symptoms.

We monitor the labs on these patients. We review treatment diaries. This is something that's done primarily by the research nurse. However, we, as advanced practice nurses, also review the patients' treatment diaries, because, many times, the patient doesn't tell you when they walk into the exam room. You can ask them, "Have you had any problems," and they almost undoubtedly they will say, "Well, no, I've been fine." But if you go back and review their treatment diary for a week ago or two weeks ago, they documented something that they're not forthcoming when you ask them in the exam room. So reviewing those diaries are very critical to monitoring that patient's ongoing treatment history.

And one of the most important roles that we as nurses — advanced practice nurses, pharmacists, and all of us — is encouraging that patient to remain compliant. Now, who among us hasn't had a patient who decided that, "Well, I think if I take three of these tablets, if that's good, two should be just as good." So, they may themselves dose-reduce themselves, which we strongly discourage from beginning throughout and to the end of any treatment. We always tell the patient, "Never adjust your dosing on any medication." Every single time there's any patient encounter, well it, whether it's on MyChart, whether it's by phone or in-person, we are always encouraging drug compliance, because we try to explain to the patient the rationale for that. "You won't get the full benefit of the treatment if you don't take it as it is prescribed. There is a reason why drugs are prescribed in the manner in which they are, and there's a reason why they are prescribed in the combinations that they are prescribed in." So, again, we all work together to encourage the patients to adhere to the written protocols that they have been given.

Slide 67: Manage Survivorship Clinics

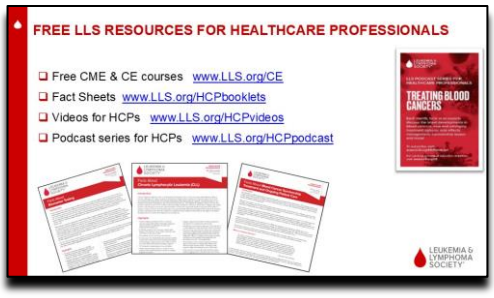
One of the other roles that I wanted to hone in on, and this is a recent role for our Leukemia Department and is specifically, at this time, for CLL patients. We do plan to expand this to other types of leukemia. However, at the moment, we know that CLL patients have a less than optimal immune system. So, therefore, we had started some time ago to collect data and review how well these patients are getting their recommended vaccines and immunizations; and we know that these patients are at risk for secondary cancers or other cancers outside of the CLL. So, we also monitor how many of them are also getting their prostate screenings and mammograms, and skin screenings.

I can't tell you how many times I talk to patients — well, every time they come to clinic — they are asked, "Have you seen a dermatologist? When was the last time you saw a dermatologist?" Because we know that they're at higher risk for skin cancer. So with that being said, we came together as a working group within our department and created a Leukemia Survivorship Clinic, which is run by myself as a advanced practice nurse and a

registered nurse. Of course, all of the clinic is overseen by an oncologist within our department.

So, the survivorship clinics provide care to patients who have either, are in remission and have completed their therapy or they are still MRD-positive, but they are stable and have had no need for acute treatment and just need to be monitored and on observation. So, these are prime patients for the survivorship clinic. And we also try to get across to the physicians, as well as the patients, that survivorship begins with a cancer diagnosis. It, survivorship does not start when you're done with treatment. It starts the day you are diagnosed with cancer. You become a survivor. And the purpose of the survivorship clinic is to monitor for current cancers, to monitor for relapsed CLL, to monitor preventive care and encourage screenings, and it's most importantly for surveillance. Again, this is a clinic and another instance where the RN works closely with the advanced practice registered nurse to continue care for the CLL patient.

So, those are some of the roles and responsibilities of the nurse, the oncology nurse in caring for CLL patients. I hope you have gained some insight into what this role is and how we work together as an interprofessional team for the best possible outcomes in our CLL patient population. Thank you.



Slide 68: FREE LLS Resources for Healthcare Professionals

Lauren Berger: Thank you Drs. Wierda, Paul, and Broadway-Duren for your very clear and informative presentations. I am now pleased to share free resources for you and your patients. The Leukemia & Lymphoma Society offers free CE & CME online webinars such as this one, in-person regional programs, and a podcast channel for healthcare professionals, where you can listen to discussions on treatment, side effect management and more. New and interesting topics are added every few weeks. Access these, as well as videos, as well as fact sheets for HCPs @ www.LLS.org/CE

Slide 69: FREE LLS Resources for Patients

LLS Information Specialists are highly trained Oncology Social Workers and Nurses who provide accurate, up-to-date disease, treatment and support information, including financial. Patients can contact them directly, or you can complete a Referral form. Information Specialists can also help you order free copies of materials to give to your patients. LLS offers free nutrition consultation to patients and caregivers with any cancer diagnosis in a 30-minute phone call with one of our registered dietitians. Contact them using the link or

phone number listed here to refer a patient. Our Clinical Trial Support Center Nurse Navigators are RNs and NPs with expertise in blood cancers. CTSC Nurse Navigators work one-on-one with patients, via telephone, to provide user friendly information, help find appropriate clinical trials, personally assist them throughout the clinical trial process, and provide information for the patient to bring back to their healthcare professional. They also work with healthcare professionals. This is unique service from The Leukemia & Lymphoma Society. I hope you will consider all of these specialists as an extension of your team.

Slide 70: Here to Help: LLS Commitment

Here is a brief overview of the Clinical Trial Support Center Process for supporting patients. The goal is not to enroll every patient into a trial, rather, to increase opportunities for participation by facilitating informed decision-making and minimizing logistical barriers for the patient. They work in collaboration with the patient's healthcare team to decide if a clinical trial is right for them. Ultimately, they educate, support, and empower patients to be active participants in, and have control over, their treatment decisions.

Slide 71: Free LLS Resources for Patients and Caregivers

LLS offers blood cancer disease-specific information and support resources for patients and caregivers, including telephone and web education programs, videos, podcasts, and booklets. I encourage you and your colleagues to stay up to date on the availability of LLS' Financial Assistance programs, and other resources, using links in these slides.

Slide 72: Free LLS Resources for Your Patients

Through targeted and culturally appropriate programs and services, we are committed to addressing needs of minoritized communities impacted by a blood cancer and those facing barriers to optimal care. Our booklets are available in English and Spanish, and our Information Specialists and other specialists consult with patients in additional languages. I hope this information will be helpful to you as you care for your patients. If you would like more information for yourself or support for your patients, please contact an Information Specialist at LLS at 800.955.4572 www.LLS.org/support

Slide 73: Thank You

Thank you to our presenters and thank you to everyone listening.