Slide 1 - CLL: Update on Treatment and Side Effects Management
Operator
Greetings and welcome to the **CLL: Update on Treatment and Side Effects Management** Telephone and Web Education Program.

Slide 2 - Welcome and Introductions
It is now my pleasure to introduce your moderator, Lauren Berger.

**Ms. Lauren Berger**
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Our special thanks to Dr. John Byrd and Ms. Kimberly Holt for sharing their time and expertise with us today.

The Leukemia & Lymphoma Society (LLS) exists to find cures and ensure access to treatment for blood cancer patients. For more than 60 years LLS has helped to pioneer innovations, such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients.

To date we have invested over $1 billion in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside. We are also the leading source of free blood cancer information, education, and support, and we touch patients in their communities through our 61 chapters across the United States and Canada.

LLS acts as the voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them to navigate their cancer treatments, and ensuring that they have access to quality, affordable, and coordinated care.

We’re fortunate to have as our presenters today, Dr. John Byrd, one of the nation’s leading experts in chronic lymphocytic leukemia, and oncology nurse, Kimberly Holt. We appreciate their dedication to supporting our mission and their commitment to caring for patients with blood cancers.

I am now pleased to introduce Dr. John Byrd, D. Warren Brown Chair of Leukemia Research, Professor of Medicine, Medicinal Chemistry and Veterinary Biosciences, and Director, Division of Hematology, Department of Medicine at the Ohio State University in Columbus, Ohio.
Ms. Lauren Berger
Dr. Byrd will speak first, followed by Ms. Kimberly Holt, Patient Care Resource Manager at The James Cancer Hospital, and Solove Research Institute in Columbus, Ohio. Dr. Byrd?

Dr. John C. Byrd
Thank you very much for inviting me to be on this and for everybody being here. In the next 25 minutes or so, I'm going to go through an update on treatment and side effect management of some of the new and exciting therapies that we have coming forward for CLL.

Slide 3 - Disclosures
So, let's get started. I have no relevant financial disclosers or commercial interests disclosed that I'll talk about today, nor does Kim.

Slide 4 - Current CLL Therapy Landscape 2015
We are going to talk about new therapies today that are coming forth relevant to CLL (Chronic Lymphocytic Leukemia).

Slide 5 - Chronic Lymphocytic Leukemia
Chronic lymphocytic leukemia is the most prevalent adult leukemia that we see in practice. It's defined by a typical immunophenotype described on flow cytometry. Patients with CLL typically are older, with the median age being 72 at diagnosis. And only 10% of patients are under the age of 50. It's more common in men.

One of the things for practitioners, nurses, and others to remember is that this is an Agent Orange associated cancer. So, when we see patients with CLL the first time, we always ask them about their military history, and if they served in Vietnam, we direct them to the VA where they can get benefits for this, which often includes a tax free supplement of up to $3,000 to $4,000 a year in free healthcare.

CLL is commonly associated with familial disease. About 10% of patients will have a first degree relative with the disease, although we don't have very many genes associated with this like we do in breast cancer and colon cancer and other diseases, although this is an active area of research.

Slide 6 - Initial Work-up of CLL Patients
So, when we're seeing CLL patients at diagnosis, we generally work them up with flow cytometry, interphase cytogenetics, looking for deletion 17p and 11q and IgVH mutational status. And these tests help us to tell how patients are going to do. There are high-risk patients that have 17p and 11q or IgVH unmutated disease, and this will
Dr. John C. Byrd
tell us that they are going to progress often quickly, within three years of diagnosis, whereas others who have mutated or have favorable FISH (fluorescence in situ hybridization), such as the 13q, may live for decades and not require therapy. At diagnosis, unless patients are symptomatic with abdominal symptoms, I don't do CAT scans, nor do we do bone marrow biopsies in the absence of cytopenias.

Slide 7 - Complications of CLL
So, it's important when seeing CLL patients initially, to talk about the complications, and these are often the things that CLL patients will die from or have significant morbidity from. This includes infections, autoimmune complications, secondary cancers, and Richter's transformation. And directing patients toward the LLS Patient Education Book is very helpful because details about these complications, what to watch for, and how they can be prevented are described to the patients, and again, this is something our team does when we're seeing a patient the first time.

Slide 8 - When to Treat CLL Patients
So, let's move on to treatment - when do we treat CLL? And essentially, while there are IWCLL (International Workshop on CLL) 2008 criteria from Dr. Hallek, and the NCCN (National Comprehensive Cancer Network) guidelines, really, when we treat CLL is when patients become symptomatic, or if they have something that's gonna absolutely drive them to being symptomatic very soon, such as enlarged lymph nodes to greater than 10 centimeters, a very big spleen, or cytopenias. And the cytopenias that are listed here and that are in the guidelines are just that, guidelines.

If patients aren't symptomatic and they have a hemoglobin of less than 10 or 10.5, I wouldn't necessarily treat them. The one thing that is not currently an indication for treatment is the white blood cell count, lymphocyte count, or lymphocyte doubling time. This was taken out of the criteria for requiring therapy, and really, I don't treat patients just based upon the count, unless their count is over 300,000.

Slide 9 - How to Differentiate Patients for Treatment
In the U.S. and in Europe, when we're seeing patients who need treatment, we treat the disease, as I said, when it's symptomatic, irrespective of genetic markers, but how we decide treatment of the symptomatic patient in part is based upon age, and CIRS (Cumulative Illness Rating Scale) score. So, in Europe they use CIRS score. In the U.S., they often use age, and as well, the genomic features either having 17p or favorable markers such as IgVH mutated or deletion 13q. I am going to go through this as I would for a U.S. patient where we're dichotomizing based upon age and genomics factor, although in Europe often the CIRS score is used.
Dr. John C. Byrd

Slide 10 - CLL8 Study Design
So, for a newly diagnosed symptomatic patient who’s under the age of 65, the CLL Light Study was very informative in randomizing between fludarabine, cyclophosphamide to fludarabine, cyclophosphamide, rituximab, and this is a study now that has extended follow-up of up to six years, and the results really changed practice.

Slide 11 - Summary of German CLL8 Study
The addition of rituximab to backbone chemotherapy of fludarabine and cyclophosphamide significantly improved response, progression-free survival and overall survival. And this three drug therapy was a beneficial therapy in terms of all these endpoints, except for the deletion 17p in patients who had normal karyotype by FISH.

Slide 12 - Recent Data to Consider Decisions
However, now there are recent studies to consider, including long-term follow-up from MD Anderson and the German CLL Group, as well as the CLL10 Study and ibrutinib data with 17p, which we'll discuss, that are relevant to this group, that potentially have the chance to change practice and what we will recommend.

Slide 13 - FCR300: PFS by IGHV Mutation Status
So, the first is this graph which looks at the FCR regimen initially piloted by MD Anderson. And what you see is, when you break these groups down based upon IgVH mutated versus unmutated, the unmutated patients, which have less favorable prognosis, all progress with time, whereas the mutated patients, at about nine to ten years, have a plateau where relapse does not appear to be occurring.

And so, this suggests that for younger patients with IgVH mutated disease, the favorable kind, that we might be able to cure them or at least induce a ten year plus remission with FCR therapy. And this is really informative to what we recommend to patients.

Slide 14 - CLL10 Study: FCR vs BR in Front-line
What about the CLL10 Study? And this is a trial that randomized between bendamustine-rituximab versus FCR alone. And many practitioners in the U.S. sort of jumped to the conclusion that bendamustine-rituximab was going to be better than FCR, as did the Germans. And I think everybody thought that these were going to be at least similar, and that bendamustine-rituximab would be much better tolerated than FCR.
Dr. John C. Byrd

Slide 15 - CLL10 Study: FCR vs BR in Front-line
And this is sort of why we do the clinical study, because as we show here, when the results came out, what a surprise that FCR was actually better than bendamustine-rituximab in terms of progression-free survival. There was a little bit more cytopenias and infection with FCR, although, when you looked at the bendamustine-rituximab arm, you really could not show any genetic group that benefitted that had this abnormality. And so, really, if we're going to use chemoimmunotherapy in younger patients, FCR should still be viewed as the standard of care.

Slide 16 - Ibrutinib: A Potent Irreversible BTK Inhibitor
The last point that I'd like to touch on is a drug called ibrutinib, which is an irreversible BTK inhibitor that is already bioavailable, and it came into clinical trials, and the results in clinical trials were better than anything that we've seen with 17p.

Slide 17 - Progression-free Survival by Cytogenetics (FISH) in Relapsed/Refractory Population
I show the relapsed data here from an updated paper by our group and other investigators, where 17p patients in a refractory setting have a better outcome, approximately a 28-month progression-free survival, which is at least a year better than what we would expect to see with anything in even frontline 17p. These data and other data from Adrian Wiestner's group led to this being FDA approved as initial therapy for CLL.

So, when we're seeing a young patient, what we typically would do in this setting is, if they have favorable markers, they would get FCR, if they have 17p, they would get ibrutinib, and then the group in the middle, I think it's the choice of whether you do chemotherapy with FCR or some other non-chemotherapy-based treatment based upon data that's coming forward.

Slide 18 - Approaches to Consider in Elderly Population
Well, what about the elderly? Here we would define patients as elderly as 65 to 70 years of age. Several studies have shown fludarabine-based regimens are not beneficial to this group, and for a long time, either bendamustine-rituximab or chlorambucil-rituximab or steroids and rituximab were used in this setting. Although recently, a nice, randomized study from the German CLL Group comparing adding obinutuzumab to chlorambucil changed therapy here.

Slide 19 - CLL11: Study Design
In this diagram I show the CLL11 study, which randomized GA101 or obinutuzumab plus chlorambucil to chlorambucil alone to rituximab plus chlorambucil.
Dr. John C. Byrd  
Slide 20 - CLL11: Response and Toxicity  
This was a large phase 3 study, and the results are summarized in this slide, which show that the response was higher with obinutuzumab and rituximab as compared to chlorambucil, and there was a higher CR rate with chlorambucil plus obinutuzumab than the other two therapies. Toxicity was fairly similar except there were more infusion events with obinutuzumab as compared to rituximab. Infections were similar between the arms.

Slide 21 - MRD Comparison and Impact on Outcome  
What about outcome? And this shows, first of all, that you saw more MRD negative or minimal residual disease negative with obinutuzumab plus chlorambucil as compared to rituximab plus chlorambucil, 25% versus 2.5%. If you were MRD negative, you did much better.

Slide 22 - R-Clb vs G-Clb: Progression-free Survival  
This gets to the meat of the study. In the top blue line, you see the progression-free survival with obinutuzumab plus chlorambucil versus the inferior rituximab plus chlorambucil, and we saw the same thing with chlorambucil alone. So, there’s an advantage to both this regimen over chlorambucil and chlorambucil plus rituximab.

In my mind, if we're treating a patient over the age of 65, or if he's not fit, this represents probably the best standard therapy for patients. People are a little uncomfortable. Obinutuzumab is a new drug, whereas rituximab is an old drug and the concern is that it costs a lot more. And in our hospital, this costs about $3,000 more for the whole course of therapy. In the world of oncology drugs today, $3,000 for an extra year of remission is probably one of the cheapest therapies that we can give to our patient.

Slide 23 - My Approach for Patients > 70  
So, how we approach our patients over the age of 70 is, we typically do our interface cytogenetics in bone marrow. We consider a clinical trial. And just like in the younger patients, if they have deletion 17p, we generally will give ibrutinib monotherapy based upon the data that I showed you. If they don't have 17p, my favorite regimen is obinutuzumab plus chlorambucil, although you can give bendamustine-rituximab. There’s not randomized phase 3 data. It's harder to give, particularly to elderly patients. And it's not my favorite thing, but it's probably acceptable to give. I generally don't give rituximab, alemtuzumab or chlorambucil or rituximab maintenance in this population.
Dr. John C. Byrd

Slide 24 - Considerations for Relapsed CLL
Moving on to considerations for relapsed CLL, again, how patients are going to do at this time point depends really upon how long they were in remission and what therapy they had. And again, we follow the same precept that we don't treat patients unless they're symptomatic. We repeat interphase cytogenetics at the time of relapse to be sure that things haven't changed. And if they have cytopenias, we look for myelodysplasia, particularly if they've had FCR, because myelodysplasia is quite common in the relapsed setting. We consider transplant, although only if unfavorable risk factors are present and generally only after patients fail or their disease relapses after a kinase inhibitor.

Slide 25 - Past Salvage Regimens for CLL
This looks at past regimens that were used in CLL, and I'm not going to talk about these for any period of time, because really, in the setting of relapsed CLL, we should not be using any of these regimens over a few of the therapies that we'll talk about a little later.

Slide 26 - Non-ablative Allogeneic Transplant
Again, about transplant, this offers a chance to cure patients, and with non-myeloablative approaches, it only carries about 10 to 20% mortality, although the majority of patients that are cured or have long-term remission will still have chronic graft-versus-host disease, which can be worse than the disease itself. And so, generally, now that we have these kinase inhibitors, such as ibrutinib and idelalisib, I generally like to see patients either being intolerant or progress on these if they have high-risk disease before going on to transplant, although I refer most of my patients for transplant evaluation.

Slide 27 - Targeting BCR Signaling
So, what we're going to talk about for the next 10 minutes or so is probably the most exciting thing that has hit the field of CLL, and that is the B-cell receptor antagonist therapy. There are two of these agents that are FDA approved that I will focus on: ibrutinib and idelalisib, which targets Bruton's tyrosine kinase. We talked about ibrutinib earlier, and idelalisib targets PI3 kinase, the delta isoform that's specific in CLL.

You know, there are other ways you can target this pathway through SYK. There's an agent GS9973, WIM and other members of this kinase. But, really, PI3 kinase delta and Bruton's tyrosine kinase are the most mature.
Dr. John C. Byrd

**Slide 28 - Ibrutinib Pivotal Phase II Study**

I talked a little bit about ibrutinib earlier on, that it's an irreversible BTK inhibitor. So, by being irreversible, you can give it once a day. It had a very, very safe profile going through its phase 1. And a pivotal phase 2 study was done, 132 patients, 31 were greater than 65 or older in the de novo setting, and the remainder had relapsed and had refractory disease. And these were really tough patients to treat. They had a median of four prior therapies, and the majority were advanced. More than a third had deletion 17p.

Two doses were looked at, although the results with both doses were the same. It is very important for people in practice to recognize that these drugs cause lymphocytosis early in therapy, but generally then people will resolve their lymphocytosis.

**Slide 29 - Adverse Events Observed in ≥ 15% of Patients**

The long term follow-up of this phase 2 that was recently published in Blood looks at the early toxicity. And again, what you see is diarrhea, nausea, fatigue, and a lot of these are disease related things. The diarrhea is a little bit more common in untreated patients, as are some of the arthralgias and other things. And this is something that we see as we move this forward. But, still, this is a very well tolerated drug. You'll see most of these are grade 1 and grade 2.

**Slide 30 - Adverse Events Observed Over Time**

When we look at the long term follow-up of this, which we just reported in Blood, you see that, really, all the side effects that occur early on pretty much go away with the exception of hypertension, which becomes a little bit more common as people stay on therapy. And I can't comment in other places, but I can comment in Ohio, that this often correlates with people gaining back weight, getting healthy again and perhaps eating a little bit too much, and with that, their hypertension comes back.

**Slide 31 - PCYC 1102 Best Overall Response**

This looks at the response of ibrutinib in the phase 2 study, and again, you see across all the groups, the response is 85 to 90%. And this occurs slowly over time. Ibrutinib, like wine, gets better with time. We see the response going up with time, and most patients have responded.

**Slide 32 - Ibrutinib Progression-free Survival**

I showed this curve earlier, and this is an updated curve looking at the progression-free survival with 30 months median follow-up, and you see that the genetic groups dichotomize, so the 17p’s do hit their median at 28 months. But, 11q and non-11q are doing quite well. If you really look at the non-11q, non-17p, their risk to relapse is very
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similar to the patients receiving this de novo, so you can see really durable remissions with this.

**Slide 33 - Phase III Resonate Study in Relapsed/Refractory CLL**

This led to a phase 3 study, the Resonate Study, which compared ofatumumab to ibrutinib. The response was higher; the progression-free survival and the overall survival all favored ibrutinib.

And it worked across all genetic groups. The value of a randomized study, though, is it informs us of toxicities that can be specific to a treatment where you really can't sort that out in a straight phase 2 study. And indeed, atrial fibrillation, grade 1 and 2 bleeding, and rash and blurred vision were seen more commonly with ibrutinib, although for all of these, this was generally manageable. Patients didn't have to go off therapy, whereas with ofatumumab, peripheral neuropathy, particularly numbness around the lips, was observed more frequently. And this is something we've seen in other studies with ofatumumab, which interestingly, hasn't been reported in the studies with it.

**Slide 34 - Important Management Points About Ibrutinib**

As we're thinking about managing ibrutinib, if you see an early lymphocytosis with this, it generally will go up, sometimes within the first week, and then it will fall over time, sometimes taking though a year or two years.

We do see bleeding and ecchymoses with ibrutinib, but major bleeding is uncommon unless you give patients warfarin. Then patients can have a lot of problems with bleeding. And you can see some spontaneous subdural hematomas. You need to hold ibrutinib three to seven days before a major surgery and then after. While atrial fibrillation comes up in about 6% of patients on this, you can leave patients on ibrutinib. I generally don't add warfarin, but I will substitute a full aspirin unless patients are at high risk for embolic disease. If they're at high risk for embolic disease because of a mechanical valve or something, then I will use idelalisib.

Something that we've seen with further follow-up is that arthralgias, panniculitis, erythema nodosum can come up on ibrutinib, and this can come up early, but can also come up late. We're seeing it sometimes in patients who are three and four years out if they're still on the drug. This can sometimes respond to a Medrol® Pak. But, there's a small number of people that have to come off because of this.

But, really, a very, very, very, very important thing for everybody to remember is that with drug, if patients are benefitting from it, you continue it. It follows the path of Gleevec® as opposed to chemotherapy where we stop it. Some of the data that is also
Dr. John C. Byrd

coming out suggests that people are stopping this because the patient's disease is getting better, and this is different than chemoimmunotherapy, that if you stop the drug, particularly in the setting of relapsed disease, just like with Gleevec and CML the disease will come back.

Slide 35 - Future Questions and Application of Ibrutinib in CLL

There are some future questions that we can consider with ibrutinib moving forward: using this in symptomatic, asymptomatic untreated CLL, asymptomatic high-risk patients, and in combination strategies, and identifying resistant disease.

Slide 36 - Ibrutinib in Previously Untreated CLL

These data show the benefit of ibrutinib in untreated CLL. And what you see is that the patients in the untreated setting do very, very well. The progression-free survival at 30 months is 96%. And there are a variety of ongoing phase 3 studies comparing this. And similarly, the Germans and others are doing early intervention trials for high-risk patients.

Slide 37 - Combination Strategies in Ibrutinib

What about combination strategies? These are ongoing here to try to increase the complete remission rate and in the setting of a clinical trial, to eventually get patients off of drug, although that's a research question right now. And I would emphasize, again, if you're going to start somebody on ibrutinib, they should stay on it.

Slide 38 - Management of Ibrutinib Resistant Disease

Well, what about ibrutinib resistance? Well, fortunately, we've been very blessed that we don't see this very often. But, when we see it, it typically occurs in two patterns with Richter's during the first year, and certainly, one reason you don't want to stop ibrutinib is because when you stop it, you can see a flare that almost looks like Richter's, but it's not. If you continue following people, things will get better.

But, for true bona fide Richter's, with diffuse large B-cell lymphoma, these patients do quite poorly. And we're still working on how to manage this. But, again, this is just about 5% after ibrutinib in the relapsed and refractory setting.

For the late relapses, usually occurring after a year, these are all mostly with CLL, and they almost always have a C481S mutation where the drug binds to the BTK enzyme or the PLC gamma 2. And in these patients, if you see this clone coming up, and it can be monitored with a blood test, or it's obvious the patient's progressing, we generally continue the ibrutinib. We don't stop it until we're ready to move on to another therapy.
Dr. John C. Byrd
And there has been one paper by MD Andersen saying there's not life after ibrutinib failure, which really, we don't agree, because there's a lot of other targeted drugs, but these are patients that really should be managed in a CLL subspecialty clinic because it's still quite rare. We're blessed that we've not seen very many relapses after ibrutinib.

Slide 39 - Representative Male Patient on Ibrutinib Developing Resistance
Well, this is an assay that we're using in our practice, and what you see in red, over time is, we're following, in the CLL cells, for the presence of a C481S mutation. And at the arrow up at top is where the patient actually showed clinical relapse. But with this assay, we could pick up relapse in the blood approximately seven months early, which allows you to add therapies to try to get rid of resistance.

Slide 40 - Idelalisib (GS1101, CAL101) in CLL
So, I'd like to next move on to the other kinase inhibitor that's FDA approved this past year, idelalisib. It targets PI3 kinase delta. And the phase one study with this also showed dramatic activity, 91% spleen and nodal response. You get the same peripheral lymphocytosis with this, but it generally doesn't resolve as much with idelalisib. So, the overall response, because of persistent lymphocytosis, is around 24%.

Progression-free survival with this is 18 months, and it's probably a little less durable with 17p than ibrutinib, although these haven't been compared.

The toxicity with idelalisib is mainly early grade 3 and 4 transaminitis, which can occur in about 5 to 10% of CLL patients in the setting of relapse. It's more common in the untreated settings. And this usually occurs during the first couple of months, two to three months, whereas late hypersensitivity pneumonitis and rash and colitis can occur with this. This can be quite frequent if people are on the therapy for a longer period of time.

Slide 41 - Study 116: Randomized, Double-blind, Placebo-controlled Trial
The phase 3 study that led to this being approved combined rituximab with idelalisib versus rituximab alone. This was a blinded study, and then patients who progressed on the rituximab alone could get idelalisib at a later time.

Slide 42 - R-Idelalisib for Relapsed CLL: Outcome
Again, these are relapsed and refractory patients, and this just shows that the overall survival and progression-free survival are much better with the addition of idelalisib to rituximab as compared to placebo with rituximab.
Dr. John C. Byrd

Slide 43 - Where Does Idelalisib Fall in CLL Therapy?
So where does idelalisib fall in the therapy of CLL as shown here? It's a reasonable therapy, although, in my own opinion, it's probably not as good a drug, namely because of the toxicity, the monitoring that's required for this, and perhaps the efficacy, particularly for the 17p patients, although these have not been compared, and until they're compared, we won't be able to say that definitively.

Another disadvantage of this is you have to give it with rituximab, although you could probably give it without the toxicity issues. For patients that need a kinase inhibitor, that need to be on anticoagulation or are at higher bleeding risk, this is my drug of choice, because you have a higher risk of bleeding with ibrutinib. This is mainly where I use idelalisib. Its ability to treat ibrutinib refractory patients is still under study.

Slide 44 - Chimeric Antigen Receptor T-cell Therapy
In the last couple of slides, I want to talk about a therapy that the University of Pennsylvania has brought forward called CAR-T therapy, CAR-T receptor therapy or chimeric antigen receptor-T therapy, where they take the cells out of the body, they engineer them to fight the CLL cells, and then they give them back.

Slide 45 - Outcome of CAR-T Cells
The response with this approach has been very high in pediatric ALL, and kudos to the LLS who supported this work by Dr. June. The data in CLL have been less optimal, although some patients have had durable remissions. But, this is not an easy therapy. You get really bad fever and cytokine release, and the potential need for immunoglobulin long term. I believe the future of this will be giving it with ibrutinib, because you make it much more applicable to CLL, and there's the potential to diminish the side effects.

Slide 46 - Other Novel Agents in CLL
There are a variety of other novel agents in CLL coming forward, including the PI3 kinase inhibitor duvelisib. There are two second generation BTK inhibitors that have properties that might be superior to ibrutinib, ACP-196 and ONO-4059. Venetoclax -- I've not talked about that. That targets BCL2, and that's an incredibly active drug. Selinexor, which is an export 1 inhibitor that's active against large cell lymphoma and Richter's transformation in clinical trials for that, and then as we talked, a variety of monoclonal antibodies.
Dr. John C. Byrd

Slide 47 - Important Conclusions
In concluding, I’d like to say select genomic studies can assist in risk stratifying our new patients, a CD20 antibody chemoimmunotherapy offers a survival advantage for both young and older CLL patients, and really, in my opinion, we should not be giving chemotherapy alone to any CLL patient at this time. It should either be a CD20 antibody with chemotherapy or a targeted therapy or a kinase inhibitor.

Patients with deletion 17p who require therapy don't respond to chemoimmunotherapy, and these should receive ibrutinib. And kinase inhibitors such as ibrutinib, and to a lesser extent idelalisib, are really altering the natural history of CLL, and really are changing this disease to what I remember CML being like several years after imatinib into the clinic; that less and less people are receiving chemotherapy, and hopefully, the future for CLL patients is going to include life without chemotherapy, and hopefully life without symptoms from their CLL that goes as long as if they didn't have it.

So, with that, I'll end my presentation and turn things over to Kim.

Ms. Kimberly A. Holt

Slide 48 - Living Well With CLL
Hello, everyone, and thank you, Dr. Byrd.

Slide 49 - Objectives
I'm going to talk briefly about managing potential side effects of treatment, aiding your patient and the caregiver in treatment adherence, and tips on the survivorship challenges of CLL.

Slide 50 - Common Side Effects of Newer CLL Therapies
So first, I have listed some of the common side effects of the newer CLL therapies. Dr. Byrd reviewed several of these closely, but just to bring out some of the more important points again with ibrutinib is the increased risk of bleeding. I've highlighted here that due to the increased risk, you do want to make sure that you have the patient hold the ibrutinib three to seven days prior to procedures, depending on the complexity of the procedure.

Some of the other side effects are often seen with other chemotherapies, as well, so you would still intervene as you would with the other chemotherapies. We did want to mention, with the ACP-196 headaches, that caffeine has been very helpful with patients with these headaches, so having them drink a Coke® or taking some Excedrin®, that has been pretty helpful.
Ms. Kimberly A. Holt

Key tips to take away with this is to educate the patient on the potential side effects and what the onset looks like, checking to see when does this start, if it's getting worse, basically seeing where it is and also ruling out other possibilities. If it's not the medication, what else could be causing this? You want to teach your patients to monitor their temperatures and signs and symptoms of infection. Also, we educate that upon starting any new therapy, the patient should be instructed to call their physician if they notice any new symptoms that occur while on treatment.

Slide 51 - Aiding Patient/Caregiver in Treatment Adherence

In aiding the patient and the caregiver in treatment adherence, I have a little graph here that shows how many prescriptions are prescribed, and then by the time you get down to how many people actually filled those at the pharmacies and then actually take them properly, and then when they refilled, you're down to a 15 to 20% compliance with taking a prescription.

A few tips here to look at when considering the cost of the medication to the patient. We noticed that this is huge with some of the newer therapies. They can be very costly. So, it's good to inquire if the patient is able to afford co-pays, and also to look into medication assistance programs. The patient should be thoroughly educated on the purpose of each medication in their treatment regimen and including any other meds that are also prescribed for prevention. This will help with compliance.

The patient should be taught that even if they feel well, to still take their medications, and specifically, we see this so often with pain medication and nausea medication. Sometimes patients stop taking something that is scheduled because they're feeling better and then notice that it's reoccurring. So, a lot of times, that scheduled med may be holding it at bay, so we try to teach about this often, as well.

And then lastly, to educate the patient to call their physician's office when running low on specialty medications because it can take a while, especially something like ibrutinib. It can take several days to reprocess and get it shipped out to the patient.

Slide 52 - Tips on Survivorship Challenges of CLL

We want to give a few tips on survivorship challenges of CLL. Because this is a chronic condition, survivors must continually monitor, and when needed, treat the disease. Survivorship is a joint effort between the patient, the caregiver, and the healthcare team. We definitely want to stress this, even though a patient may come to a specialty clinic, such as what we have here at The James and other areas, we stress with them to maintain a good relationship with their local providers, as well.
Ms. Kimberly A. Holt
And then to use whatever resources they can to be able to contact their physician, the nurses, the dietitian, social workers, all of those on the team. You want to stress to your patients that they are in reach.

The healthcare team should be easily accessible to the patient. You want to clearly communicate your best contact numbers so the patient knows that if they do have any new symptoms or any questions, they can call and contact.

You also want to encourage the patient to connect with other CLL survivors or other cancer survivors. There are many survivorship programs out there; support groups. We have several patients who meet up at our clinics on blogs, they've met each other through blogs, and it's been a good support for them. And then we've mentioned here some of the events such as The Leukemia & Lymphoma Society's Light the Night, and Pelatonia, which is here locally in Ohio.

Slide 53 - Tips on Survivorship Challenges of CLL
And then a few more tips on survivorship challenges are to remind your patients to maintain their health and wellness by keeping follow-up appointments as scheduled, even if they're feeling better. A lot of times they can call in and reschedule after reviewing their status, but to keep the follow-up appointments. We also advise to maintain preventative health screening such as colonoscopies, dermatological and gynecology appointments, as having CLL and then being treated with therapy can put patients at a greater risk for a secondary cancer.

We also remind them to keep up with annual vaccinations such as flu, and every five years with the pneumonia vaccination -- no live vaccines. We advise patients also to aim to avoid contact with persons who have known infections. Once again, having CLL can put that patient at greater risk for infection, and then depending on what type of treatment they're getting, as well, that would be increased; and, as always, good nutrition, staying active and exercising, and getting plenty of rest.

Slide 54 - CLL Resources
I've included here for everyone's review some slides on CLL resources, so you can take your time and look through here. There are websites, and there are also phone numbers. The Leukemia & Lymphoma Society is awesome, not just because they're providing this program, but for our patients. We literally reach out for their medication assistance, travel assistance, and as you can see here, there are education programs and support groups. They also have a peer connection link, so there are so many different things.
Ms. Kimberly A. Holt
There are also flight services through Air Charity Networks, and we've listed some websites here. They have volunteer pilots who will fly patients that are receiving specialized treatments to appointments for free.

Slide 55 - CLL Resources
And we mention lodging assistance and a few general cancer websites for you to go to. I personally also appreciate chemocare.com because it has patient friendly chemo education and great instructions on managing side effects.

Slide 56 - Medication Assistance Programs
And lastly, there are also the medication assistance programs, as Dr. Byrd has mentioned Imbruvica® or ibrutinib and Zydelig® or idelalisib. You'll see the specific sites there for helping with co-pay assistance, and then we also have mentioned The Leukemia & Lymphoma Society.

Slide 57 – References
This concludes my presentation.

Slide 58 – Thank You
Ms. Lauren Berger
Thank you, Dr. Byrd, and thank you, Kimberly, for your very clear and informative presentations.

Slide 59 - Question & Answer Session
It is now time for the question and answer portion of our program. And we'll take the first question from the web. This question is from Pamela. "What is the reason for the spike in lymphocytosis with BTK inhibitor therapy?"

Dr. John C. Byrd
With ibrutinib, one of the ways it works is to make the CLL cells less sticky in the bone marrow and in the lymph nodes where the CLL cells like to live. CLL, when it can't stay in the lymph nodes and the bone marrow, it goes into the blood. And that's a mechanism-based effect that occurs with ibrutinib and several of the other B-cell receptor inhibitor agents.

Ms. Lauren Berger
Thank you. And we'll take the next question from the web audience also, and this one's from Nancy. "What do you think of Zydelig alone?"
Dr. John C. Byrd
I think Zydelig alone for CLL is probably an adequate therapy. The benefit of rituximab is not clear right now. The company has done most of their studies combining the two, but it's not clear that rituximab significantly adds. And I think that's a fine therapy, particularly if it's part of a clinical trial.

Ms. Lauren Berger
Thank you. And we'll take the next question from the telephone audience please.

Operator
Our next question comes from Steven calling from Louisiana. Please state your question.

Steven
I'm 58, diagnosed about a year and a half ago. My question is, is there any advantage, in your opinion, these newer drugs--I don't have any symptoms right now, and I know FCR is not really considered standard any more if you don't have symptoms. What is the general thinking about just as preventative or prophylactically treating early with no symptoms?

Dr. John C. Byrd
That's a great question. Right now we wouldn't do these as preventative outside of a clinical trial. There are clinical trials, and we have one that's going to be starting at The James very soon that's looking at getting these agents early on for the treatment of untreated CLL who are at high risk for their disease becoming active. But, outside of a clinical trial, we wouldn't do this.

Ms. Lauren Berger
Thank you for your question, Steven. We'll take the next question from the web audience, and this one's from Sheila. “Can you please explain the difference between CLL and B-cell lymphoma, like marginal zone, particularly the type of lymphoma which has spleen and bone marrow involvement?”

Dr. John C. Byrd
Well, lymphoma and CLL are two different diseases, although there's one type of lymphoma called small lymphocytic lymphoma, which is CLL. It's just where it exists in the lymph nodes. And so, the testing that we talked about, the immunophenotyping or the flow cytometry, can often differentiate marginal zone lymphoma, which can be in the blood, can be in the bone marrow and the spleen from CLL. And this is a specific test that the doctor has to do in the clinic to differentiate these two.
Ms. Lauren Berger
Thank you for the question, Sheila. We'll take the next question from the telephone audience please.

Operator
Our next question comes from Marsha calling from Washington. Please state your question.

Marsha
Yes, I'm confused about the IVIG replacement. In my course of CLL in 13 years, it's been replaced below 700, then it went to 400, then I was told there was a formula dividing the 400 in half and replacing below 200, then I'm told there's a shortage, and I'm very confused on this. Please address it.

Dr. John Byrd
I think everybody is a little confused about where IVIG should be used, because all of the studies that were done with this were done before we had the new drugs and CLL patients are now living longer. Really, the right patient to use IVIG on is not something that's completely agreed on.

Where we would use it is in a CLL patient that's had a lot of problems with infections or very, very life threatening infections that didn't have a lot of symptoms before that, like meningitis that we could observe, as Ms. Holt said, by following for fever and other things and intervene with antibiotics.

We generally make our decision to start IVIG based upon that and not a number, because most patients with CLL will have a low number, and a lot of them don't have a lot of problems with infection. And so, you could avoid using IVIG.

Kim, do you want to add anything?

Ms. Kimberly A. Holt
It's just another time if a patient is noticing that, as Dr. Byrd said, they are having more infections or noticing that they're around the people who are having more infections like someone in the family that is repeatedly having issues, they should notify the team about that, and once again, checking those IgG levels. And I think currently the magic number is 600. At least here with our patients and with our insurances in Ohio, we've noticed that the magic number seems to be 600, if it is outside of infection.
Ms. Lauren Berger
Thank you for your question, Marsha. We'll take the next question from the web audience, and this one's from Brian. Brian asks, “Is there potential cure with targeted therapies?”

Dr. John C. Byrd
So, our hope is that, with these new drugs that we have coming forward—we talked about ibrutinib and idelalisib, with venetoclax, that giving all of them together—we're about to start a trial at The James where we're giving ibrutinib, venetoclax and obinutuzumab, the new CD20 antibody together, that we can induce minimal residual disease, negative disease and potentially get people off of therapy and into remission.

Right now, though, the only curative therapy that we have is allogeneic stem cell transplant, although, the CAR-T cell therapy that Dr. June and others are doing at the University of Pennsylvania that was supported by the LLS, offers a chance of cure there.

Ms. Lauren Berger
Thank you for your question, Brian.

We'll take the next question from the web audience, and this one's from Edith. “When is watch and wait not appropriate for CLL Stage 0? Would any specific markers cause you to recommend treatment?”

Dr. John C. Byrd
There are no markers right now that would cause me to recommend therapy outside of a clinical trial.

Ms. Lauren Berger
Thank you for your question, Edith. The next question is from the web audience from Tony. Tony asks, “Please talk about past research on the use of green tea extract and also on the importance of checking the patient's vitamin D level prior to starting their treatment.”

Dr. John C. Byrd
We'll do the second one first. So, vitamin D is commonly low in CLL patients. And there have been a couple of studies that suggest that that may be associated with more quick progression, although it's not clear. Certainly, whether you have CLL or you don't have CLL, and I'll raise my hand and say that I was in this club because it's awfully cold here in the winter, replacing vitamin D is probably a good thing if your vitamin D is low because it can boost your energy. And for some people, it may be the cause of the
Dr. John C. Byrd
winter doldrums. But it’s not something that clearly has been shown to be associated with progression or poor treatment outcome and it’s something that’s being studied right now in clinical trials.

To actually get the benefit of green tea, you would have to drink multiple gallons of green tea. And there are tablets that you can take. Those have been studied in the setting of clinical trials. And for low risk patients, they may slow down the pace of the disease a tiny bit, but this was often looked at in patients who probably were not going to require therapy anyway.

And so, it’s certainly safe. It causes GI upset and liver function abnormalities every once in a while, but it’s something that can be taken as long as you’re getting it from a reputable place.

Ms. Lauren Berger
Great. Thank you Tony, for your question. We’ll take the next question from the web audience, and this is from Wynona. “In your practice, are PMN values shared with patients, and of what significance does this have to treatment and longevity? How reliable are purge cell values in estimating longevity?”

Dr. John C. Byrd
We do give the white blood cell count and the neutrophil counts in our practice to patients. We try to do it as quickly as we can, because they’re often nervous about the count. In terms of predicting outcome, it’s not clear that they’re predictive of outcome, though, unless they’re being associated with infection.

Ms. Lauren Berger:
Thank you. The next question is from the web audience from Renee. Renee asks, “How many patients develop celiac disease after treatment for CLL, and who should inform the patient?”

Dr. John C. Byrd
I think I’ve seen that once in my entire practice, so it’s pretty rare. Once it occurs, one doesn’t want to give the same therapy again, if it was something that induced that. But again, that’s something that’s very, very rare.
Ms. Lauren Berger
Okay, thank you for your question, Renee. We'll take the next question from the web audience. This one's from Steven. “With the new agents, what is the current thinking in regards to using them on newly diagnosed CLL patients that are still symptom free?” That's similar to another one.

Dr. John C. Byrd
Yes. So, in the setting of clinical trials, that's a worthwhile thing. But, outside of clinical trials, it's not something that we would do.

Ms. Lauren Berger
Okay, thank you for your question, Steven. The next question is from Anna. “Is there a correlation between CLL and autoimmune disorders? If so, would you recommend these be treated separately or concurrently?”

Dr. John C. Byrd
There is a higher association of hematologic autoimmune complications, such as autoimmune hemolytic anemia and ITP, with CLL. And typically, we will treat the underlying autoimmune problem, and often, if the CLL is active, the treatment that we use for that, either steroids or rituximab, will fix the CLL for a period of time. And if that happens, then we don't move on to treat the CLL.

Ms. Lauren Berger
Thank you for your question, Anna. We'll take the next question from Katherine. Katherine asks, “As a nurse/patient, I would like to know how to find current, up-to-date resources in chemotherapy options, hematologic research and other therapy options.”

Ms. Kimberly A. Holt
So, we did try to include that on one of our slides. The Leukemia & Lymphoma Society has been awesome with their website. You guys are awesome with your website for some of the more up-to-date treatment, some of the new emerging therapies that are out there. We also included the American Cancer Society. There are a few websites that we've listed on our Resource slide that provide more resources that are available for patients with CLL.

Ms. Lauren Berger
And I'll just add to that that these slides will be up on the website afterwards at www.LLS.org/ce, so you can access them then. And also, The Leukemia & Lymphoma Society's Information Resource Center is a place to go. You can call or email for help on searching for a clinical trial, and they'll do an individual search for a clinical trial, as
Ms. Lauren Berger

well as provide both written and oral information on some of the new treatments and ways to get more information.

Dr. John C. Byrd

And Dr. Brian Koffman writes a very good blog and has a patient website, where he addresses a lot of questions that patients have early on with CLL, so that's another resource.

Ms. Kimberly A. Holt

At The James Cancer Hospital, we have a lot of clinical trials here and some of the newest therapy. People call in a lot to our hematology line, which I could actually provide. But, for CLL specifically, our main hematology line is 614-293-3196. And we do have people call in to ask about clinical trials.

Ms. Lauren Berger

Thank you. We'll take the next question from the telephone audience please.

Operator

Our phone question comes from Melissa calling from Ohio. Please state your question.

Melissa

Hi, Dr. Byrd. I was wondering, since a lot of these small molecules work on BCR signaling, do they have application in lymphomas, such as mantle cell and follicular?

Dr. John C. Byrd

So, these drugs like ibrutinib are active in mantle cell lymphomas. Ibrutinib is actually approved in mantle cell lymphoma. And it's active in follicular lymphoma and some of the other B-cell lymphomas. And idelalisib, as well, is active in follicular lymphoma and the other types of lymphoma. It's probably not as active in mantle cell lymphoma.

Ms. Lauren Berger

Thank you for your question, Melissa. We'll take the next question from the web audience, and this one's from Ronald. “Would you still recommend ibrutinib in conjunction with either BR or FCR for an elderly patient who relapses after receiving chlorambucil first-line, then two years later BR?”
Dr. John C. Byrd
I would never at this point, for a relapsed CLL patient, give chemotherapy. I believe that ibrutinib or idelalisib have superior results to really all of the salvage therapies that we've utilized and that's a better therapy for patients. It's more in terms of side effects and also efficacy.

Dr. John C. Byrd
There was a study addressing, “Does ibrutinib add to the benefit of bendamustine-rituximab?” at ASCO (American Society of Clinical Oncology), the national cancer meeting that just finished earlier this month. The answer to the study was that ibrutinib added to bendamustine-rituximab, but when compared to how patients that received that three drug combination did, it was identical, or maybe not even quite as good as the phase 2 trials that I showed giving ibrutinib alone.

There's really not a reason that chemotherapy needs to be given as a salvage therapy for CLL in my opinion.

Ms. Lauren Berger
Okay, thank you for the question. The next question is from the web, and Sharon asks, “Do we know if ibrutinib loses effectiveness if the patient goes off of it and then back on it if necessary?”

Dr. John C. Byrd
That’s a loaded question. We don’t know the answer to that. But, I would say with what we know and how ibrutinib has been studied to this point, as long as you’re tolerating it and it’s controlling your disease, you should continue it. And doctors, sometimes, who are less informed, will see things get better and say you can stop it, and that’s not how these drugs were studied, and that would not be something that I would do.

So, if you’re intolerant to it, you’re having side effects with it, then in clinical trials there are other BTK inhibitors that are being tried in that setting, or you could switch to idelalisib. But, I wouldn’t stop these therapies if they’re working because that’s not how they’ve been studied to this point.

Ms. Lauren Berger
Thank you for your question, Sharon. We’ll take the next question from the web from Tredell. “For a newly diagnosed patient 82 years old with congestive heart failure, what would you recommend?”
Dr. John C. Byrd

If the congestive heart failure is really, really symptomatic and associated with heart disease, and again, not having seen all of the data, doing a gentle therapy. This might be a setting where I would do chlorambucil by itself, but really, this is a complicated case that really seeing all the information and doing a consult would be necessary.

You want to say something about how complications can intervene with therapy?

Ms. A. Kimberly Holt

Sure. So, basically, having other comorbidities or complications, that's when it really is time to see a hematology specialist, especially if you can, a CLL specialist, just because when you add all of these pieces together, and then the different medications that a patient may already be on and other side effects, you just need a more dedicated eye to it. So, in this setting, also, we would definitely have a patient contact the office more to stay in touch if any symptoms do change or if they do start therapy, based on the other comorbidities.

Ms. Lauren Berger

Thank you for your question, Tredell. And thank you all for your questions.

Slide 60 - Resources to Make Informed Treatment Decisions

Special thanks to Dr. Byrd and Kimberly for your continued dedication to patients and for sharing your time and expertise with us today. If we were not able to get to your questions today, please call The Leukemia & Lymphoma Society's Information Specialists at 800-955-4572 from 9 am to 9 pm Eastern time, or you can reach us by email at infocenter@LLS.org.

The Information Specialists are available to answer your questions or your patients’ questions about treatment, including clinical trials, or questions about support, including financial assistance for treatment.

Dr. Byrd and Kimberly, thank you again for volunteering your time with us today. On behalf of The Leukemia & Lymphoma Society, thank you all for joining us. We wish you well.