Improving Outcomes for Patients With Chronic Lymphocytic Leukemia

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JENNIFER WEBSTER Good evening and welcome to this certified dinner symposium. My name is Jennifer Webster. Now it is my great pleasure to introduce your speakers for this evening: Ms. Amy Goodrich and Dr. Mazyar Shadman. Ms. Goodrich is a nurse practitioner in the hematologic malignancies program and researching nursing manager at the Johns Hopkins Kimmel Cancer Center in Baltimore, Maryland. She manages patients with various types of hematologic malignancies, concentrating on the lymphomas. She also manages the Cancer Center's research nurses and is extremely involved in research operations. Dr. Shadman is an assistant member at Fred Hutchinson Cancer Research Center and an Assistant Professor of Medicine at University of Washington. He is a hematologic malignancies expert who specializes in treating patients with lymphoma and chronic lymphocytic leukemia. Please join me in welcoming them both here.

MS. GOODRICH Thank you for being with us this evening. We are not going to stand at this podium as we are going to be going back and forth and for us to be jumping up and down is a little awkward, so we are going to do the presentation from here. We are here to talk about CLL this evening. These are our disclosures. Our learning objectives: We are going to talk about new agents, emerging therapies in CLL, risk stratification and the appropriate treatments for

patients based on risk stratifications, and then we are also going to be talking about adverse events and managing adverse events.

CLL/SLL. CLL is the most common leukemia in the western world. These are the criteria for diagnosis of lymphocyte count greater than 5,000. The typical immunophenotype includes CD5 and CD23. This is typically a disease of older folks. Certainly, it can occur in younger patients, but most of these people are going to be older, considered indolent, and of course, those of you who see these patients know that every patient is different, every disease trajectory is different.

This is just a contact slide of mature B-cell neoplasia and where CLL fits into that piece of the pie. Presenting symptoms. You are seeing these patients. You know that most patients have no symptoms. They usually have a painless enlarged lymph node, or they had bloodwork done for their preop visit or some other random thing, but there are a host of other presenting symptoms, but really most patients will not really have a lot of symptoms. Most patients are well otherwise. It is just stumbled upon. The diagnostic workup for those of you who are seeing these patients and doing that diagnostic workup, peripheral blood flow is absolutely a stand-alone diagnostic test for these patients. Of course, they need a good exam and a good set of blood work including hepatitis screening. Bone marrows are completely optional. For your younger patients' fertility considerations. You don't see scans on here, so you scan based on the patient in front of you and whether that's appropriate or not. There are all sorts of additional

things that may be appropriate, but this is the 100% every person who gets diagnosed should have these things done and then you tailor from there.

Molecular biomarkers for CLL. Unfavorable, absolutely unfavorable 17p deletion or TP53 mutations. And I like to say, I don't care what malignancy you are talking about, whether it's myeloma or colon cancer or anything, TP53 and 17p are never good. It holds true in CLL as well. Some of the others are complex karyotypes. 11q deletions are also unfavorable. On your FISH studies, trisomy 12 is a neutral and certainly 13q deletion, as well as mutated IGHV status, is favorable, so then of course unmutated is an unfavorable. If you are looking at a diagnostic workup, after you have established the diagnosis, really getting these studies, the FISH studies, the karyotyping, and next-generation sequencing really are important. The next-generation sequencing is important because some CLL can be 17p deletion negative but have TP53 mutation, so you miss some of those if you don't do both of those tests. The prognostic value of these FISH tests are here. Of course, your 17p patients really have a very different trajectory than your 15q patients. That just reinforces why these FISH studies are so important and we will talk about how this can change over time, so continuing to do those intermittently because patients can have evolution of those.

Staging. So, Rai is the staging system we use here in the United States. Zero to 5 based on counts and extent of disease, organomegaly, bone marrow failure.

These are the updated 2018 iwCLL guidelines to initiate therapy. This is really important, and these are important things for patients to understand too,

that there really are criteria for when to start therapy. We do a lot of hands off with CLL. This can be really difficult, for patients to know that they have a malignancy and not be treated, so it is really important for them to understand the triggers, the internationally recognized triggers for starting therapy. Before starting, everybody should be meeting the criteria, they should be having TP53, FISH – I talked a little bit about that and just making sure you have all your studies done prior to starting therapy.

DR. SHADMAN Basically what has changed in the markers we just reviewed in terms of mainly prognostic markers, there are two factors to look at. One is disease and one is the treatment that we are using to treat that disease. Some of these markers that we reviewed are really meaningful in the era of chemotherapy and we are kind of officially past that era almost. That table that showed chromosomal changes including 11q and things like that, they are no longer considered to be high risk when we use these novel agents.

And what other novel agents do we have these days? This slide basically summarizes all the new drugs that are approved or will be approved in the near future or expected to be approved for CLL. If you look at the left panel, you have this B-cell receptor, and you can think of it as an engine that runs the CLL. Basically, CLL cells are dependent on this ongoing activity of B-cell receptor, without the mutation, without any rearrangement, it is just an ongoing activity of those cells. One idea to block that engine is to go for the enzymes that are downstream of that receptor. Here you have BTK, or Bruton tyrosine kinase. You have PI3 kinase on the left side. Depending on which enzyme you block, we

have different drugs. For BTK, we have BTK inhibitor, ibrutinib, which was a true game changer for CLL, and we may have another one coming soon. Acalabrutinib is a drug that is in the guidelines for some selected CLL patients, but not yet approved by the FDA for CLL, so those two drugs block the Bruton tyrosine kinase enzyme. For PI3 kinase, we have two inhibitors. One is idelalisib. This is a drug that was approved back in 2014 in combination with rituximab for CLL, and more recently we have duvelisib, which is also another PI3 kinase delta and gamma inhibitor. We have four drugs that are considered B-cell receptor inhibitors. What's common with these four drugs, and in general with B-cell receptor inhibitors are a few things. For example, when you start these drugs, you see this initial lymphocytosis, which is a very normal and expected clinical finding. We see that with ibrutinib, acalabrutinib, idelalisib, and duvelisib.

We will talk about the studies that led to the approval of these drugs and some of the more recent studies. On the right panel, you have venetoclax, which is a drug which works totally differently. Cell death is a planned process in our body cells, and in cancer cells what happens is that plan is not implemented. BCL2 is antiapoptotic protein. It stops cells from dying. If there is a way to stop that protein, or block that protein, basically what you are doing is helping the cell to die, and if that cell is a cancer cell, that's a good thing. Venetoclax is a drug that blocks an anti-dying protein in a CLL cell. For that reason, it helps with the cell death. Since these drugs very differently – venetoclax works very differently compared to ibrutinib or acalabrutinib or other drugs, there is a rationale for maybe combining them. These are the novel drugs that we have for CLL.

The question is – Amy just showed you the indications for treatment – we really treat patients if there is a reason for treatment. If they have low blood counts, if they have large lymph nodes, or if they have symptoms related to CLL. We have guidelines and numbers, but really it is common sense. When CLL is affecting someone's life, we need to treat it. The question is: why do we have to wait that long? The answer so far has been we have tried, we have given chemotherapy at the time of diagnosis, it just doesn't help. We don't help patients live longer. The next question that comes from the patient is yes, you tried with chemotherapy, what about the new drugs? That's the question that you are trying to answer, and there are studies that are already published or presented, and there are ongoing studies. This is kind of an active area of research. One of these studies that tried to answer this question is called the CLL12 study, done by the German CLL group. What they did basically, in patients that don't need treatment by standard criteria, they came up with a scoring system that defined high-risk patients. There are so many scoring systems that are really beyond the purpose of this talk, but let's agree that these patients were high risk by molecular or clinical factors. What they did is they randomized those patients to receive either ibrutinib or receive placebo. The idea was to see what happens in terms of the outcome. What you have on the right side is event-free survival care. Meaning, that if a patient dies, or if a patient relapses, or if they had a symptomatic relapse, not just a rise in lymphocyte, that would count as a failure and you would see a drop in that care. Patients that took ibrutinib compared to patients who did not take ibrutinib had a better event-free survival. Most of us

agree that in this setting, in a patient who would normally not need treatment for maybe 5, 6, or 7 years sometimes, the only reason to start somebody early on treatment is if you can prolong their life. This study is not showing that. We are not seeing an overall survival benefit from starting ibrutinib. The study is designed in a way that is statistically powered to find that survival benefit with longer falloff, so we have to wait for it. But as of now, this will not change our practice. For ibrutinib at least, based on this study, we still follow the standard iwCLL criteria and wait until they need treatment. It is a very common question you are asked in the clinic: why don't you start me on a pill that is easy to take, and I just start taking it? There is no meaningful clinical benefit.

There is a study that will be opened to accrual and it is an intergroup study that is designed and will be run by SWOG group with basically the same concept. You define high-risk patients and you either start them on venetoclax and obinutuzumab, which is a CD20 antibody, and we will talk about it briefly at the time of diagnosis, or when you see them; or in the other arm, you just wait until they meet standard criteria. The idea is to see if you can help these patients live longer. This, as you can imagine, will be a very long study in terms of follow-up. These days, fortunately, CLL patients do not die from disease, or if they do, it will take a long time, but at the same time this study will require a long follow-up. We need to wait for this study. The point is, right now we still follow the guidelines that we used to follow.

What are the options for frontline treatment of CLL in patients? We talked about these prognostic markers and we mentioned the 17p deletion. So, what is

17p and what is p53? p53 is a target for most of the chemotherapy drugs. What happens with chemotherapy drugs, we induce stress inside the cell, and when the cell senses this, it activates the p53 gene, which is another apoptotic target. It basically tells the cell that there is a lot of stress going on, I can't handle it, let's die. That's what the p53 gene does. That happens if you have a functioning p53 gene. If you have a deletion in that area, and that p53 gene does not exist, or if you have a mutation where you have the gene, but it does not work very well, they can be under a lot of stress, but they don't die because that mechanism is not in place. Because of that p53 mutation or deletion—let's call it p53 aberration, or abnormal p53—we should absolutely not use chemotherapy in these patients. We will have it in the table, but one of the take-home points should be that the reason we emphasize so much on checking FISH and checking for molecular tests to look for the p53 abnormality is that those patients don't need chemotherapy. You will see soon it is very rare for a CLL patient to need chemotherapy period, but there are still physicians or patients that may ask for chemo. So 17p or p53 deletion, absolutely no chemotherapy. So here we are looking at patients who do not have an abnormal p53 gene; their p53 gene works. What are the treatment options? You have left and right columns looking at the fit and young patients on the right and a little bit of old or frail patients on the left side. No matter which group you are looking at, your options are either ibrutinib or a single agent, or a combination of venetoclax and obinutuzumab. This is based on the NCCN guidelines. If you are familiar with the NCCN guidelines, there is a category of recommendations there and ibrutinib has

category 1 recommendation, and venetoclax/obinutuzumab combo does not. The category in the NCCN guidelines is based on the voting of the members—what percentage voted yes to that regimen. But those two options are both reasonable and we can talk about some of the thought processes and what are some of the factors that will affect us making a decision of one of the two options.

Other recommended regimens: You see pretty much everything for CLL. You do not see FCR on the left side, because older or unfit patients should not receive FCR. We will talk about the studies that led to this, but just to give you the big picture, treatment recommendation for first line, basically we are talking ibrutinib or venetoclax. In the case of venetoclax, it is given with a CD20 antibody.

In the relapsed setting, again it would be very usual to use chemotherapy or chemoimmunotherapy these days. You have a list of medications as a preferred regimen for the relapsed setting and in the first column you have acalabrutinib, ibrutinib, venetoclax, duvelisib, idelalisib. If you remember from that slide, these are just the drugs included in that figure that explain the mechanism of action. Acalabrutinib is listed there. It is not FDA approved at the moment, but for selective patients it is used. The second column is for younger patients. Again, in the relapsed setting, because we do not use chemotherapy, again that classification may not be very relevant. The maintenance therapy I think we can just ignore. That is really just in the setting of using chemotherapy and using maintenance, and even then, we never use it. You can ignore the last column. So just to cover the 17p, we talked about the fact that they should not get

chemotherapy, and as I said nobody should get chemotherapy, but here you have ibrutinib and venetoclax. I think that order is the order in which we would go with in terms of starting with one drug. I think in this setting, ibrutinib has a much better track report and much robust data in terms of the long-term activity. And the second option is venetoclax in combination with the CD20 antibody. In the relapsed setting, depending on, of course, what you use in the first line, then you have all kinds of novel agents that we can use.

If you have a patient with a functional p53 gene. I just told you, you can choose venetoclax and obinutuzumab or ibrutinib and the question is, which one? I'll tell you what the benefits are, or advantages, or disadvantages of each. Venetoclax and obinutuzumab is attractive because it gives us the potential limited duration treatment, or finite treatment. As you know with ibrutinib, or acalabrutinib or idelalisib or duvelisib, you start the treatment and you take the pill until it doesn't work or until they don't tolerate it. It is ongoing treatment. It is like being on an antihypertensive drug, which could be okay if patients tolerate it, but we all know that tolerance and side effects can be an issue with novel drugs. These are cancer drugs at the end of the day and can be very toxic. Venetoclax and obinutuzumab, the way that this combination is studied, is just to give venetoclax for 1 year and obinutuzumab for 6 months and then stop. It is 1 year of treatment. It is not chemotherapy and it is not forever. That is very attractive. Now, that's how it's studied. The question is what happens after patients stop the 1 year of treatment. Ten years later, how many of them are still on no treatment? We don't know that. This study was just published, so the follow-up is very short.

We really don't know what percentage of patients end up remaining treatment free for a long time or for a meaningful time, but at least there is hope. The way venetoclax works in combination with an antibody, you do have that hope because at the end of 1 year of treatment, in 50% of patients, depending on where you look for minimal residual disease, in the blood or bone marrow, somewhere between 50% and 70% of patients, you won't find any evidence of CLL in the bone marrow or in the blood. That is a very important indicator for how long that patient can remain in remission. So, there is hope. We will need more follow-up, but you do not have that kind of MRD eradication with ibrutinib or acalabrutinib. That's why you don't even hope for finite duration treatment. When I have a discussion with my patients, I give them both options. I say, you have the potential to be on a treatment for a limited period of time, let's say 1 year, but you have to work on it. For the first couple of months, it is a lot of work. Venetoclax is a drug that can come with risk of tumor lysis syndrome, and it's a real risk. You have to pick the right patient. You need to work on tumor lysis risk management, maybe debulk them before treatment, watch them very closely, and between the debulking, and the dose ramp up, you basically bring your patient back weekly for 8 weeks. That's a lot of work for patients. I would say after that 2 months, it's a very easy drug to tolerate. You kind of pay the price up front and then enjoy a relatively easy drug to take after the initial storm you go through with the patient. It's a lot of work for the patient, or the physician, for my colleagues who take care of these patients at the university hospital. The tumor

lysis can happen in 2 to 3 hours in a high-risk patient. That's kind of the pro and con for that first option.

Ibrutinib is a drug that has been around for a long time. You have the most solid long-term follow-up data with ibrutinib. We just recently had the 5 years follow-up of the first-line ibrutinib from the RESONATE-2 study. There are studies from the NIH group showing very robust long-term efficacy and the toxicity profile is well understood now. There are no surprises. There are side effects with ibrutinib, but that's ibrutinib and if patients don't get those side effects like atrial fibrillation and bleeding, which is rare and something we talk about a lot but in real practice, at least in my experience, is not something I would be dealing with a lot. I don't remember, but maybe I've had one patient. So, if you tolerated this drug you just need to be okay with taking something for a long time. And a lot of patients are okay. I kind of present both options to them and I tell them there is no comparison between the two and again there are many factors. So, if somebody is not able to come back once a week, or if someone's renal function is really poor, or if they have bulky disease and I do not know how to debulk them, I would go with ibrutinib. I don't think we should talk about chemotherapy, maybe if there is a question later, I can go through it, but chemotherapy is not a preferred or even second-line choice for frontline CLL. Really the discussion should be between the two drugs.

MS. GOODRICH This is just a summary of frontline studies from the chemo era. Looking at FCR versus BR, we've got progression-free survival superior with FCR, but not overall survival, and then really no benefit for the older

patients. This is really why we were happy to get rid of chemotherapy for most of these patients. German CLL11 with chlorambucil versus obinutuzumab versus chlorambucil/rituximab, versus chlorambucil, and again you guys know this, obinutuzumab were superior for progression-free survival and overall survival. RESONATE-2, which was ibrutinib versus chlorambucil. Of course, ibrutinib was superior and I think we are going to go over a little bit of this data in a bit. What we are setting this up for is that novel agents are rapidly changing the landscape for CLL and certainly the outcomes for our patients with CLL. Again, just summarizing prognostic factors that are very critical, or that IGHV mutational status, cytogenetics, flow cytometry, getting your biomarkers done, so really this bottom bullet is so important that patients with TP53 abnormalities, for those of you who have been around the block, we used to tell patients they were going to live about a year, and now 5-year survival has improved from less than 40% to over 80% with ibrutinib alone, and now our toolbox for those patients is just getting deeper and deeper. It is not endless, but it's a whole different conversation you have with patients now versus before we had these drugs.

This is just to show you some long-term follow-up because some of these newer agents, and those of you who were around when ibrutinib hit the market, some of the really difficult conversations were about the fact that we didn't have long-term follow-up and we didn't know what the long-term or late toxicities were going to be. These are important, all these long-term follow-up studies are important for us to look at again, to look at: is the curve really staying where it

was, where it started out? Is response dropping off? What's happening with overall survival? And what are these late toxicities that are being seen?

Looking at ibrutinib with rituximab versus FCR for treatment-naive patients. I love this study. This study took patients, younger folks, no 17p deletions treatment naive, and they got FCR versus ibrutinib with rituximab. As you can see here progression-free survival was actually superior with ibrutinib and rituximab, so gets us one step closer to getting rid of chemo, because as you just heard, FCR is only appropriate in people who don't have 17p deletions, but now we know that ibrutinib and rituximab is actually superior. I love this grid looking at adverse events, so the adverse event profile is so much more attractive for the ibrutinib arm. We all know how nasty FCR can be for patients. Hopefully, that will be a dinosaur, a total thing of the past and we will say remember when we gave FCR? In the dark ages?

DR. SHADMAN I was just going to add – you mentioned the progression-free survival benefit. There was also an overall survival benefit to ibrutinib/rituximab. Patients that got ibrutinib/rituximab lived longer and that's not something we see very often.

MS. GOODRICH Right and this will be an important one to keep our eye on long-term follow-up data to make sure that actually sticks. This is really just showing the details of that trial. It is just off-the-shelf FCR, but then the details of the ibrutinib and the rituximab there, that patients started out with ibrutinib, and then they got the rituximab added to cycle 2, and they got a total of six cycles, and then cycles 8 and beyond were just ibrutinib. That just gives you

an idea of that schedule for those patients. Again, just looking at patient characteristics, which we don't need to go over, but I just wanted you to have this in your online slides to be able to look at. And then this is showing you the progression-free survival and the overall survival. Hopefully all of those, that overall survival, will continue to show that separation, but I love the idea of getting rid of FCR for everybody.

Bendamustine. This was a study that actually had three arms: it was BR, ibrutinib, and IR. As you can see here, this was older patients, newly diagnosed, and the take home here was clearly ibrutinib, but adding the rituximab to the ibrutinib, which are those two little top lines, it didn't help. So, now we are figuring out who is going to benefit from the addition of anti-CD20 with these novel agents, and who isn't. This is just showing you the difference. The younger folks did benefit. The older folks are not benefiting.

DR. SHADMAN The two studies were both ibrutinib/rituximab versus FCR and the one versus bendamustine/rituximab, they were both presented at our ASH meeting last year. To give you a little bit of background of why everyone is so excited about these two studies, before December 2018 (which is ASH) we did have access to ibrutinib for first-line patients, but that was based on a study that was a randomized study, the RESONATE-2 study, that compared ibrutinib to chlorambucil, and ibrutinib was the winner. So ibrutinib got the label for first line, so you do have the option, but talking to patients, if somebody is young and FCR kind of candidate, you would still talk about FCR and they would ask you, "Why don't you give me ibrutinib? It's approved." There were these long conversations

about what's the difference between having a label for a drug versus having a study showing that it's really the right treatment for you. There was a period of time, I guess two years or so, that we had these discussions reviewing the clinical trial data for chemotherapy versus ibrutinib, so these two studies really made it very easy for us. Ibrutinib now – if you think about CLL patients in the upfront setting, you have this young, fit, and very healthy population for which FCR used to be the option. Ibrutinib was able to beat that in the ECOG study. Then you have this middle group, not very frail, but kind of not FCR type of patients, so bendamustine/rituximab has been the historical treatment for them. Ibrutinib beats that. And then you have these very frail patients, [unintelligible] with a CD20 antibody and ibrutinib beats that with RESONATE-2, and there is another study that combined ibrutinib with a CD20 antibody. So really ibrutinib covered the first-line study going for a different range of chemotherapy regimens and it was the winner. For some of them it was prolonged patients' lives, for others was basically progression-free survival, which is an acceptable endpoint for most of our trials. Now that's the story of ibrutinib.

Before this study, which is the German CLL14 study, we did have venetoclax approved for the relapsed setting. We will go through that data. We are going from frontline to relapse, so the timing may not make sense here. So, venetoclax is approved for relapsed setting. We were not able to use it in a previously untreated patient. The study we are seeing here was a very important study because it compared venetoclax and obinutuzumab as an experimental arm to chlorambucil/obinutuzumab. Really the question was not whether or not

this combination can beat obinutuzumab and chlorambucil, but was just a study that will give the opportunity of using venetoclax in the frontline setting, like ibrutinib did when it was compared to chlorambucil. That's why this study is important. As I said, big difference between venetoclax and everything else, novel agents, is that we go for a fixed duration treatment—in this case, 1 year. Not surprising the venetoclax combo had a progression-free survival benefit. The overall survival is pretty similar, so there is no OS benefit at this point, maybe follow-up is short, maybe patients have a lot of other options if they fail their first-line setting. They can go on many novel drugs. But this was a positive study. I think what's important is number one, now we have venetoclax for all CLL patients. Number two, this table is actually very important. It shows what is the rate of minimal residual disease eradication in the bone marrow after, first row, venetoclax/obinutuzumab, based on this study. Fifty-seven percent of patients had no detectable CLL in the bone marrow. Compare that to ibrutinib and obinutuzumab combo on a different study: there you have 20%. Go to FCR: 27%. FCR used to be our strongest chemoimmunotherapy. Now, it's intention is to treat, meaning the percentage is within the patients who were positive compared to all, so if you only test 30% of the patients and your denominator is going to be the whole population, the actual number may be a little bit higher than 27%, but other studies looked at most of the patients, and the number is not even close to 57%. Really the point is this is a very strong treatment and it is not chemotherapy. The thought process is, yes, this study was done in less fit patients. The CLL14 study was done in patients who were older or had abnormal

kidney function. These are not your typical young FCR type patients. One may ask, okay why are you using that data to give venetoclax to younger patients? The answer is the treatment functions very well. It gives you 60% MRD elimination rate. Why do we think this will not be the case in a younger or fitter patient? Doesn't make sense. So, in terms of the biology it is a very strong treatment. That rationale is being used when we use this combo for the younger patients, but it's important to know that venetoclax is not yet tested against FCR or BR. I don't think it should be tested. There is a study ongoing that has the option of chemotherapy, either FCR or BR, as the standard arm, but we just showed that those are no longer standard treatments. In some cases, it is not even ethical to enroll them in a randomized trial if they may get chemotherapy. This just gives you an idea of, this is a non-chemotherapy regimen, it may be a fixed duration treatment, and it does a great job. I think that's important.

We have one slide on the combination of venetoclax and ibrutinib; just the take-home message is, it's experimental. It is not something we use in practice and we should use in practice. There is a single-arm study that was published recently by an MD Anderson group, other groups, the Ohio State group, and there are studies from pharmaceutical-sponsored studies that are ongoing. There are two intergroup studies ongoing by ECOG and Alliance groups, testing the combinations comparing to ibrutinib and a CD20 antibody. We have to wait for those studies to see if this is really ready for practice. Yes, if you combine your best two drugs together, of course you get much better results, but the question is what if patients' relapse. Then you have used all your great options up front.

Yes, if you can cure them, or if time to relapse is 40 years, yes, we don't care, but you really don't know that. So, in practice there are situations where we go with both drugs, but that's not the frontline setting at this point. If somebody fails ibrutinib and you add venetoclax to it, sometimes they keep them on both, or vice versa, but it should not be a planned treatment outside of a clinical trial.

We kind of covered that and really the decision of going with ibrutinib versus venetoclax/obinutuzumab, maybe it's worth taking a quick look, because this is a very common question these days. You have two great drugs, and okay which one is the right answer? Ibrutinib, there is long-term efficacy data. It is a very easy drug to start. You basically write the prescription and send them to the pharmacy to pick it up, assuming insurance is not an issue. Sometimes there is some delay, but it is really that easy. Tumor lysis, you do your standard protocol for tumor lysis, but it's not a known side effect for ibrutinib. In patients who logistically can't follow the ramp-up protocol, or they have significant or unstable kidney disease, or for any reason you believe they are high risk for tumor lysis, and you cannot modify it, ibrutinib would be a great choice. You had two studies showing this is a better drug compared to your best chemotherapy options and you also know that if you go with ibrutinib and if it stops working, venetoclax is a very reliable backup for you. There is a clinical trial that we will show it works in patients who fail ibrutinib. These are all reasons to go with ibrutinib.

What about venetoclax with a CD20 antibody? Obinutuzumab in this case. It is time limited. That means a lot for a lot of patients. After that initial 1 or 2 months, it is better tolerated in general and it would be the preferred choice in

patients who have significant cardiac risk factors or if they have major bleeding issues. You can argue if they are on anticoagulation. That is a long conversation, because there are other options that you can use in those settings, and you get deep remissions, which is meaningful if you were planning to stop treatment. And at least now we don't have a lot of data about what happens if venetoclax stops working. Is ibrutinib a reliable option or not? We will see some data coming at the ASH meeting soon, but these are basically factors that we consider when we think about the two options.

MS. GOODRICH So RESONATE, this is relapsed/refractory, so this is ibrutinib versus ofatumumab. In the relapsed/refractory setting, patients were randomized to get standard, open-ended ibrutinib versus ofatumumab. Of course, the ibrutinib arm is superior, as you can see, for progression-free survival. Updated results, and this is where this again is so important, at a median of 64 months, continues to be superior. I say that anybody who studies CLL and certainly follicular lymphomas, the overall survival is the holy grail and you have to be very patient. This is not a place for people who are impatient because to really get those overall survival numbers, it takes a long time now that we have such very effective therapies for these patients.

Idelalisib and rituximab for previously treated patients. This is the registration trial for idelalisib and rituximab in CLL. Patients were randomized to idela plus rituximab versus rituximab alone. Again, as you can see here, progression-free survival clearly superior with the idela and rituximab arm. Again, these new agents are really changing the landscape.

DR. SHADMAN We showed all these new drugs including idelalisib and duvelisib, but if you remember, in the first-line setting, we didn't mention anything about idelalisib or duvelisib. Those are also great CLL drugs. They are novel. They work kind of in a similar way. But why didn't we talk about them in the first-line setting? As you see in the third and fourth columns, this drug was tested in the upfront setting, in the first-line setting, in younger or even older patients. First of all, the side effects of PI3 kinase inhibitors idelalisib or duvelisib, the three big ones are transaminitis. You get this initial elevation of your liver enzymes that usually happens weeks after you start, and it usually comes back down, and you can even start patients back on the same dose. That is your first side effects. Six to 7 months into treatment, you get to this major problem of diarrhea or colitis, and I can tell you it looks like acute GVHD and you treat it like acute GVHD and it is not a situation you want to be in treating CLL these days, so it could be really, really nasty. You see those side effects are much more common if you use this drug in the previously untreated patient (that's idelalisib). Why? One theory is that those side effects are kind of immune-based side effects, or autoimmune type of side effects that are induced by PI3 kinase inhibitors and if you have a patient who is previously untreated, they have a healthier immune system because they have not seen chemotherapy and that's why they have a much more active immune system that can cause these AEs. I'm not saying that we never use them. I mean, I have never used them, but if you look at some of the guidelines by some prominent CLL experts in the world, you sometimes see idelalisib in the first-line setting too, but seeing the side

effects in the first-line setting, I would not use them in the first-line setting. You don't see them in the NCCN guidelines and there is really no reason with all the other alternatives to do that. I think that's an important clinical point to cover.

Duvelisib. I really see it as a very similar drug to idelalisib. PI3 kinase inhibitors – there are many of them right now. We have three that are FDA approved. For CLL, we have idelalisib and duvelisib. For follicular lymphoma, we have idelalisib, duvelisib, and Copanlisib, which is an IV form. Idelalisib and duvelisib are pretty similar. This is a PI3 kinase delta and gamma inhibitor. In terms of side effects, I think you see less transaminitis with duvelisib. Otherwise, expectation and looking at the numbers from the studies it seems to be a pretty similar drug. I don't know how much it is used in practice. Fortunately, most patients do so well on BTK inhibitors or venetoclax that we rarely get to the third line, but duvelisib is another option.

MS. GOODRICH Ibrutinib resistance in CLL – it almost never occurs in the first year. If it does, you need to figure out if the patient is actually taking their drug. Transformation is definitely something that is definitely seen in patients who develop ibrutinib resistance, and when resistance happens, it is usually a poor prognosis and they relapse pretty quickly. This median survival, I'm not sure that's accurate today. This is changing continuously with all the new data coming out. Resistance to BTK inhibitors – the importance of this slide is really to show you if someone is resistant to ibrutinib, acalabrutinib hooks in exactly the same way, so if somebody is resistant to one, switching drugs in this category is not recommended. Switching drugs should happen because of toxicity, not because

of resistance. About 50% who discontinue ibrutinib do so because of toxicity. Ibrutinib was our first-generation drug, acalabrutinib is our second-generation drug. And again we keep saying it is not FDA approved, although we use it all the time and it's in the NCCN guidelines. Slightly less toxicity with acalabrutinib, so switching drugs can make sense. Acalabrutinib has less AFib, less skin toxicity, pneumonitis, bleeding. Those are still risks, but they are just lower.

Why is this happening? Our first-generation drugs are always our breakthrough, but then our second-generation drugs get smarter. There are these off-target hits that ibrutinib has that cause the platelet inhibition, that lead to the bleeding, the atrial fibrillation, so as you can see, acalabrutinib has less of these things, and as these other drugs are in development, they are going to be hopefully even smarter than ibrutinib. Really, taking a great drug and making it better is what is happening here. This really shows you ibrutinib and all of the off-target hits that it has. I call them the innocent bystanders. Then acalabrutinib is much more specific to BTK, so sort of leaves some of those other normal cells alone. This is a great change here for us.

Acalabrutinib- and ibrutinib-intolerant relapsed/refractory CLL. This is a phase 2 study. There were 60 patients enrolled, and the most common reasons patients stopped ibrutinib – and this is what you are seeing in your practice I'm sure – atrial fibrillation, atrial flutter, diarrhea, rash, arthralgias, and there was a very small bleeding number there. Those patients had been on ibrutinib at least 6 months. What happened when they got switched to acalabrutinib was a great overall response rate, 72% overall response rate, so the drug is still effective.

That target's still worse for those patients. Progression-free survival not reached at 19 months. So, patients did discontinue acalabrutinib, some because of progression, adverse events, other reasons. The most common grade 3 adverse events: pneumonia, neutropenia, and count issues. Bleeding happened in 62% of patients, which is very similar to ibrutinib. Both of these drugs have a very high percentage of bleeding and it is usually minor. Three percent of those patients had major hemorrhage, and it's more like 6% with ibrutinib. And then hypertension is something that was seen as well in this patient population. So, just reasons to switch those folks if they are intolerant. Using acalabrutinib just instead of ibrutinib in the relapsed/refractory setting.

This was a phase 1/2 trial. Had 60 patients enrolled and the dose escalation – the phase 1 portion gave 100 to 400 daily and then there were no DLTs in the phase 2 dose is really what we have today, that 100 mg twice daily, which is currently the recommended dose. The overall response rate was fantastic at 95% and 100% in 17p deletion. Today we don't know what is better, ibrutinib or acalabrutinib. Time will tell because there are studies going on pitting those one against another, not using them sequentially but picking one over the other so we will have to wait and see. In terms of Richter's, there was no Richter's seen in this study, so again, more coming and only time will tell which of these – I think of these drugs as when we imatinib, dasatinib, and nilotinib and which one to use, when do you use them, how do you sequence them – this is just the tip of the iceberg of these drugs that we have today. There were some

20+ year people out there, so in your years of experience, who have lived through this before.

DR. SHADMAN In the guidelines right now, acalabrutinib is listed as an option in the relapsed setting, mainly for patients who do not tolerate ibrutinib. The question is, what about just using acalabrutinib? This is a study that was done in the relapsed setting and compared acalabrutinib as the experimental arm as you see there, versus physician's choice of either idelalisib and rituximab. As we showed, this is another standard treatment for relapse, or bendamustine/ rituximab. The primary endpoint, as you have noticed, these are pretty standard designs for most of these studies, going for progression-free survival. There was significant benefit in terms of progression-free survival in favor of acalabrutinib compared to either idelalisib or bendamustine/rituximab. There is no overall survival. We talked about how it's not surprising. A combination of short follow-up at first report and other great options in patients who relapse. Why is it important? This most likely will give acalabrutinib label in the relapsed setting, and we will see what happens in terms of FDA approval. Again, acalabrutinib is another BTK inhibitor. It is a cleaner one. It has, in the absence of a head-to-head randomized trial, just looking at the data for each drug, seems to have less side effects and numbers are not zero for atrial fibrillation or bleeding but seems to be better tolerated with fewer side effects. We did talk about the guidelines. In patients who truly fail ibrutinib, there is no role for acalabrutinib or other classic BTK inhibitors. Again, there are other drugs in clinical trials that block BTK, but

not by binding to the site that ibrutinib and acalabrutinib bind, so those are different drugs, but they are very early in development these days.

A very important study that we will have at the upcoming ASH meeting in 6 weeks is a study that has tested acalabrutinib in the first-line setting. It is a three-arm study: acalabrutinib versus acalabrutinib and obinutuzumab versus chlorambucil and obinutuzumab. The results will probably not be surprising, but again the study is important because it will give us the option of acalabrutinib in the first-line setting and then we will need to make more tables talking about ibrutinib versus acalabrutinib versus venetoclax and all kinds of discussions with the patient. I think it's great to have many great options. I told one of my patients the other day: we just have so many great drugs. I can't tell you which one is better. I can't rank them 1, 2, 3, 4, but we will get to a situation where multiple myeloma has gotten to in the past few years where you just have so many great drugs and you need to stick with the principles and pick the right treatment. There is no clear answer of which drug is clearly better. I don't think we really need to do head-to-head studies to compare these two drugs together. There are just many good options.

So, again, we are going from frontline to relapse, but timewise, actually as you know, drugs first get approved for the relapsed setting and come to the first line, so this study was a combination of venetoclax and rituximab compared to bendamustine and rituximab in the relapsed setting. This was done before the CLL14 study. Again, same principle for venetoclax, which is a finite duration. Two years of treatment in this case with venetoclax and rituximab and

bendamustine/rituximab was just the standard bendamustine/rituximab six cycles. This study was presented 2 years ago at ASH. It is now published, and we have follow-up data. There was a progression-free survival and an overall survival benefit of venetoclax and rituximab compared to bendamustine/rituximab, which has made this combo a very attractive combo for the relapsed setting. Here really the point is, I kind of covered it for the first line, you see deep responses. You see complete responses and you see no evidence of CLL in a large number of patients. I think that's kind of the take-home point from this slide and I really don't want to read the numbers for you. Side effects are – the main thing is that tumor lysis and to follow the patient closely, and get them through that first 1 or 2 months, you may still deal with some neutropenia and thrombocytopenia down the road and some GI toxicity, but again, for somebody who treats a lot of CLL patients, again after that first phase, these patients are much easier to manage and I do not see them very often, meaning that they do not have a lot of problems.

This is a follow-up publication after the original report of the study, and it kind of goes back to the point that I made when I was talking about venetoclax. You talk about 1 year or 2 years of treatment, but what does it mean with the longer follow-up. With the first line of study, it was just recently published, and we don't really have a good follow-up. This was a year before the frontline, so we have some follow-up. The real question is, in patients who finish their 2 years of treatment, then what? What happens to those patients? Do they go back on venetoclax or some other treatment 2 months later? In that case, really this

combination is not fixed duration. So, here what you see is – this is end of treatment and these are patients who had no detectible disease at the end of 2 years. Here in this box you see how we define low-level, high-level, or undetectable disease by flow cytometry. These are the patients who finished treatment and had no detectible disease. Gray, I believe, are patients who have low-grade detectible disease, and the purple are the ones who have more disease, more than 10 to -2. Then you see from each group what percentage had relapse. I can tell you with 10 months of follow-up only 12% of patients had relapse and went back on treatment, and almost all those patients were patients who had some detectable disease at the end of treatment. So, this tells you, at the end of treatment, if you are thinking about maybe this patient is tolerating the pill very well, and they are asking you should I really stop? I'm okay, should I really take it? And again, this is totally data free zone, and what I'm telling you is what my practice is. You may hear different things. What I do, I check the flow and I check for minimal residual disease. I feel much more comfortable stopping treatment in patients in whom I can't find any evidence of disease. It is not wrong to stop regardless. That is how the study was done. The study was two years and stop, no matter what your response is. It kind of tells us that MRD, or minimal residual disease assessment, is an important thing for venetoclax. We did not talk about MRD in ibrutinib, acalabrutinib, idela, it doesn't matter. If your treatment goes forever, I don't care if I have 0.0001% CLL in my bone marrow. I'm taking a pill forever, who cares? But if I am stopping, I want to know if I have active disease or not. You will see at ASH there are so many studies and there

are so many upcoming studies that go with MRD-based decisions to stop treatment, with all kind of combinations, at least for the next few years, will be the active research in the CLL. So MRD at the end of treatment matters. We know it for relapsed setting, and we will probably start getting that data for the frontline setting. We mentioned that in patients who fail ibrutinib, venetoclax works and that's based on this clinical trial, so patients who had relapsed or refractory disease after ibrutinib, and there were, as you can imagine, high-risk patients and they still had 60% overall response to venetoclax, including 10% CRs. You have a reliable backup if you start with ibrutinib, and that's really what this slide shows.

This is a very poor-quality slide because I took a picture from somebody's presentation. That tells you that there is not much data really for the reverse order. This is eight patients who got venetoclax first, went on ibrutinib, and sounds like ibrutinib works, but this is nothing compared to a really well-designed trial. The bottom line is we don't have reliable data telling us ibrutinib is a good option after venetoclax. Again, we will wait for ASH and there may be more data coming, but this is a factor to consider, especially for high-risk patients. Really, these two drugs, for standard CLL, both ibrutinib and venetoclax work so well, that I don't really think about this a lot, for somebody with 13q standard risk CLL, I know they will do well on venetoclax. They will do well on ibrutinib. They will do well on whatever I give them, but when you get to the 17p, p53, you have to be really smart. You have to pick the right sequence. There is no room for risking and there is no room for guessing. You have to go over the solid data. The best data is for ibrutinib first line. You have a reliable back up, and then you go with

the next level. I think this is really the point of the two slides. As I said, ASH will have some data with ibrutinib after venetoclax. Kind of summarizing everything in the relapsed setting, in terms of the options. I did not, really acalabrutinib should be there next to ibrutinib. Maybe it's not because it's not FDA approved yet. These are the options for the relapsed setting. The difference is now we have idelalisib. Everybody agrees that idela or PI3 kinase inhibitors are your third line, so you would probably go with a BTK inhibitor or venetoclax first and second and then idela is there for an option. Here you see the differences in terms of what is the target for each drug, the dosing, the major side effects, common side effects, and duration of treatment. I think we covered all these.

A couple of slides on CD20 antibodies. These are of course for chemoimmunotherapy, no matter, you just pick a chemo backbone and add the CD20 antibody to it, and it has been historically rituximab and there has been a lot of effort to replace that with a better CD20 antibody. We don't use chemo, so that is kind of irrelevant these days. But venetoclax is still given with a CD20 antibody, so it is important to know that CLL is a disease for which all three available CD20 antibodies are approved for: rituximab, ofatumumab, and obinutuzumab. Again, it may not be the hottest topic for CLL these days, but it used to be at some point. Ofatumumab is an option. I personally haven't used it. I either go with rituximab or obinutuzumab. But there are differences between the three. Just in general, I think for CLL, it is accepted that obinutuzumab is a better antibody than rituximab, so if you have access to it and if you can get it, I think

obinutuzumab should be used whenever there is a need for a CD20 antibody. These days, venetoclax is the best partner for it.

CAR T for CLL. First of all, CAR T therapy is not approved for CLL right now. The only approved indications for CAR T, as you know are diffuse large B cell lymphoma and ALL. There are ongoing studies, registration studies for CLL. There are published studies using efficacy of CAR T-cell therapy for CLL. So, if you think about high-risk CLL patients – and I put CAR T in the same box as allogeneic stem cell transplant as cellular therapy. So, if a patient gets to the point where I start talking about stem cell transplant, then I will always use CAR T if I have access to it before doing allogeneic transplant. These days we all know about CAR T therapy, well basically here we take advantage of a patient's own T cells and we educate them to attack the patient's tumor, and in this case, CD19 being the common target. The process involves getting the patient assessed initially and then collecting them using an apheresis process to get the T cells out. It takes around 2 weeks to finish the gene modification and transduction in the lab, and then you need to give them some kind of lympho-depleting chemotherapy, cyclophosphamide, and fludarabine. In the case of CLL, those are the FC part of FCR, so they have some anti-CLL effect as well. That's not why we use it. We just make room for the new T cells to go in. When the T-cells go in, you have to deal with the chemotherapy type of side effects, but two specific side effects from CAR T are, number one, cytokine release syndrome. We intentionally create an immune storm in patients' bodies, so that can present side effects ranging from fever, hypotension, hypoxemia, and death rate of

around 3% if you look at all CAR T studies, not just CLL. And neurotoxicity is also another side effect that you need to watch patients for. If you look at the best quality and biggest studies, we are having between 40% and 50% complete response rates at the 30-day assessment, but the long-term remissions seem to be in the range of 30% to 35%, similar to what we see with diffuse large B-cell lymphoma. The best outcomes after CAR T are seen in patients who achieve an MRD-negative CR on day 30. Everybody else tends to relapse later on. This is an important piece of information, because we should not be wasting time on a patient who gets CAR T and they still have disease on day 40; they are not going to go CR. If a patient has a high-risk disease that got through the CAR T and CAR T did not work for them, or worked but didn't have the perfect response, you should get ready for allogeneic transplant if that's an option for the patient. That's at least what our practice is and it's kind of consistent with some of the published guidelines, which are based on no data. It's just a consensus guideline.

Allo transplant. We have a long track record for allogeneic transplant. We don't use myeloablative allo transplant for CLL. It's too toxic and it causes mortality. I tell patients that there is a 50/40/20 rule for allo transplant for CLL: Long-term 50% overall survival, 40% disease-free survival, but then you have somewhere between 20% to 25% chance, unfortunately, of dying from the transplant and the complications from transplant. If you look at this table, I put different studies, transplant is a very general term. It could be based on the donor situation, conditioning, GVHD regimen, there are so many variations there. In our most recent experience where we published 200+ patients getting allogeneic

transplant for CLL, patients who did not have comorbidities – actually we had a non-relapse mortality rate was somewhere between 0% to 10%. Patient selection is key and doing the HLA typing at the right time, not waiting until patients are 84 to send them to allogeneic transplant. That's what we are seeing. For high-risk patients, ibrutinib works great and venetoclax works great, but if you have a 30 year old with a high-risk disease, at some point they will be out of options. We kind of need to pick the right time for that referral to cellular therapy consult, which would be CAR T and allogeneic transplant.

MS. GOODRICH Let's move on to side effect management. Just to roll up some of what we've talked about: ibrutinib – there is a 5x increase over the normal population of atrial fibrillation with ibrutinib. Bleeding again, there is a high rate of bleeding. Most of it is minor: petechiae, brushing your teeth and bleeding. Hypertension. I can't remember if we have the slide on long-term follow-up, but that rate increases as patients stay on ibrutinib. The hypertension is an initial problem but really over time becomes more of an issue. One of the most important things I think are the diarrhea, because that's the life-altering thing for patients. I tell people take it at night; when their gut is shutting down, they tend to have less nausea and diarrhea. I always say this lymphocytosis, in some ways that's the most important teaching point for your CLL patients who come with their 10-year graph of their lymphocyte count. They really need to be prepared for that or it is, I say, potential psych admissions for some of these patients.

This is over time. I don't know how many of you have seen this data. I was so happy when this came out, but this is really showing over time – look at the

hypertension rate, really goes up over time, and we are not necessarily thinking about ibrutinib being the cause of that, but it is, and I am not sure you would stop it, but just to take credit for this happening to patients. I will let you look at this, but really some of them stay flat over time, and some of them really vary, especially the atrial fibrillation/atrial flutter as time goes on becomes a little more prevalent even though those numbers are low overall. And then hyperglycemia. These were really some eye-opening trends to see and keep in mind with your patients who are on ibrutinib. Again, I don't think you are going to stop the drug if it's working, but just to know that you are contributing to it.

Acalabrutinib. Some of the different things with acalabrutinib: headaches and weight gain, sort of like the edema issue with imatinib, dasatinib, nilotinib, sort of that same family of peripheral edema. Special considerations for BTK inhibitors: PML has been seen, other infections. I will always call it PCP because I am a 20+ year-er. Infections due to hepatitis B reactivation, we have to be aware of that for many of these. We talked about lymphocytosis. Second primary malignancies, those also occur with this family of drugs, so keeping that in the back of your mind. I think there is more data coming out on the pace of those second malignancies, and I have seen some of those, patients who develop another malignancy that just takes off, but I think we need more long-term follow-up data on these. Then headaches, again much higher with acalabrutinib than ibrutinib. Hemorrhage and bleeding. As you can see here, our first generation versus our second generation, so slightly lower risk of bleeding, slightly lower risk of atrial fibrillation/atrial flutter, and then hypertension is not such an issue at this

point with acalabrutinib, but again we keep saying not FDA approved, so we will see as these data get more mature.

Has anybody not given venetoclax? Okay, so the name of the game with venetoclax is the ramp-up. The tumor lysis syndrome; in early clinical trials they started out giving the full dose of 400 mg and there was fatal tumor lysis syndrome, so now this ramp-up. If anyone has not seen that ramp-up packet, it's beautiful. It's color coded. There's a calendar. No matter what kind of learner you are, patients can't mess it up. They do 20/50/100/200 and then it's week 5 they get up to their full 400 mg dose. All dose escalations require some level of tumor lysis monitoring and I think initially that was scary, but we have all gotten used to it because this is such a good drug that we are all using it.

CYP3A inhibitors. If you don't have a pharmacist or a mechanism to do a good medication review, all of these drugs have huge lists of drug-drug interactions and I feel like it's those of you in the room who have the best relationships with patients to really understand what medications they are actually taking and what they consider to be a medication versus something they get at the GNC, but certainly tumor lysis syndrome, they should all be on allopurinol, being hydrated, and some patients should be admitted. I really talked about most of this. The most common adverse events: neutropenia, diarrhea, URIs, aches and pains with venetoclax, and some count changes. This is, if you have never seen this, this is the roadmap for who can and should manage as an outpatient and who needs to be admitted for tumor lysis monitoring. I have had no issues getting insurance companies to pay for admissions for people to have

that ramp-up and it is sort of alarming. I don't want to say alarming; it is a new routine for your inpatient teams to have somebody come and take a pill and get intensive tumor lysis syndrome monitoring. But since that ramp-up has been adopted, there have been no fatal tumor lysis syndrome events, so it works if you follow the ramp-up.

DR. SHADMAN I think this is a very important drug. More recently it has label for all CLL patients. Initial indication was limited to 17p patients in the relapsed setting. Now it is basically for everybody with CLL. I think there are so many practical points, and at least in my institution, my colleagues are doing all the heavy lifting for this. Really important to know that as we get used to using this drug, it becomes very easy to say, "Oh yeah, tumor lysis is there but it is not a real problem." I have seen, and there are reports that groups or people may skip the ramp-up. That should not be done. The ramp-up should absolutely be followed. What happens with the tumor lysis with venetoclax is that it can happen very quickly. Actually, there is a good reason for monitoring these patients in the inpatient setting overnight. I always call the night person and tell them why this patient is being admitted, because, as you said, people are just not used to somebody taking a pill and then tumor lysis. As you know, inpatient could be you get a TLS lab at 4 p.m. and the next one is, before you know, is at 6 a.m., so there is a 12 hour. So, I make sure that they get the draws and there is data that shows that uric acid may not be a good marker for tumor lysis monitoring. So, the night person looks at urid acid and it's normal and they kind of – I have a patient who was started on vanc and piperacillin and tazobactam with some electrolyte

changes and hypoxia overnight just because uric acid was normal and initially they did not think about tumor lysis, but on a closer look, their phos went up and their potassium. So, the whole panel should be monitored closely. If it happens – it's not very common, but in high-risk patients with high white count, with kidney problems, they could be on medications that could have a major interaction with venetoclax. I always tell my patients don't think that a simple drug may not interact with venetoclax. Every time these patients are seen, I go through their medication list and make sure that I check for interactions or I talk to my pharmacist because if TLS happens, it happens quickly. It happens in 2 hours and the cases could be really sick in a few hours and then in the ICU if they are inpatient. So, the drug interaction could be a major problem if you don't look at it.

MS. GOODRICH Safety of PI3 kinase inhibitors – we did talk about this. The PI3 kinase inhibitors, for those of you who were at the immunotherapy talk, they alter T regulatory cells that are responsible for self-tolerance, just like the checkpoint inhibitors. They have very checkpoint inhibitor–like side effects. It's all from that T-cell manipulation, so the 'itises, early tend to be liver toxicity: transaminitis, bilirubins can be elevated. Initially is very garden-variety diarrhea, and then later 6, 7, 8 months the patient has developed colitis. They can develop pneumonitis. All those 'itises you are thinking about with checkpoint inhibitors can happen with these drugs, and there are recommendations for monitoring and how to dose reduce. There is also an infection risk with these drugs as well. These are sort of a unique oral drug, we don't really think of oral drugs as causing checkpoint inhibitor–like toxicity, but these do.

We've got some case studies here. A 72-year-old male diagnosed 5 years ago, with early-stage CLL, 13q deletion, IGHV mutated, no TP53 abnormality, so a good prognosis patient, lives alone. He's got some hypertension. His lymphocyte count is slowly increasing. He is becoming thrombocytopenic. He's got new fatigue and some night sweats. So, thinking about this patient, what additional testing does he need? What are his treatment options? You should always think about, if patients don't have a 17p, or TP53 abnormality – I don't know what you do if they have them. We don't really check them again. If they don't have them, you always have to be thinking about them. So, before you start therapy in patients who don't have a documented 17p, or TP53, you should be repeating those to make sure that you understand because you see that the treatment options are different. All the chemotherapy goes off the table if they do have those high-risk features. So, he gets some repeat studies done. He's got still his 13q, he's got new trisomy 12, but TP53 continues to be negative. You always have to think about transformation with these people as well, so that's where imaging becomes important. There is nothing on CT that's alarming and certainly no reason for a PET. So, this guy splits his time between you and Florida. He doesn't want to go on a trial. You talk to him about ibrutinib versus venetoclax and obinutuzumab. He doesn't want to do IV therapy. He decides he wants to do ibrutinib. He develops an initial lymphocytosis, some diarrhea and nausea. It improves with good supportive care. His white cell normalizes. His adenopathy does a huge reduction. He remains on ibrutinib. So, year 3 he calls you from Florida. He is in the hospital for atrial fibrillation and worsening

hypertension. So, what are you going to do? You hold his ibrutinib, he requires cardioversion for atrial fibrillation, he's on three antihypertensives for blood pressure control, he's responding to ibrutinib, but clearly, he's having some pretty severe late toxicities. This is where you are going to talk about other options. Do you switch classes? Do you keep him on a BTK inhibitor and just switch him to acalabrutinib? This is where you could consider rituximab with venetoclax because that's now second line, two years of therapy. This guy really wants to be able to move freely between. We all have these people who are snowbirds. He just wants to be on a pill, so he is going to get switched to acalabrutinib, because he is not resistant to ibrutinib, he is just intolerant. He does well with it and remains on acalabrutinib. These are patients you are going to see because up to half of patients will stop ibrutinib because of toxicity.

DR. SHADMAN Fifty percent of patients who stop ibrutinib stop it because of toxicity.

MS. GOODRICH Case study 2 is a 60-year-old female with deletion 17p. She has got a mutated mutational status, otherwise healthy. She has been on ibrutinib for 4 years because she started monotherapy all those years ago. She presents with progressive disease, lymphocytosis, new nodes. So, what does she need? Does she need FISH testing? She's got a 17p deletion. You could, but you don't really have to because it's not going to get worse than that. Do you need to know her TP53 status? No. She's got a 17p deletion. You don't really need to repeat. Once you have these high-risk features, you don't need to keep repeating. Does she need imaging to rule out transformation? She does.

Because this is a risk of ibrutinib, and she's got new nodes. What are her treatment options? If you look at the NCCN guidelines, she's got several options, but she's a youngish lady and our toolbox is not endless, so it is time to refer her to a transplant center. Her best options are venetoclax and rituximab versus PI3 kinase therapy that is only indicated in two lines or more, but we really do talk to patients about all of these drugs because tomorrow the indication may change. So, she's going to go on venetoclax and rituximab. She meets criteria for medium-risk tumor lysis syndrome. This really is important to look at this and understand whether people need to be admitted or not. It sounds goofy, but I do this. And all of you, these are well-tolerated drugs, but we are the ones who are going to keep the patient safe and so really understanding her risk is important. She starts allopurinol, she has her tumor lysis labs done. This is actually very common, that patients will develop some changes in their labs. So, for those that do, you have no way of knowing whether that creatinine or that potassium is going to continue to head up, of whether they are going to plateau here and go down. You really can't try to manage these people as an outpatient. Once they really start trending toward tumor lysis syndrome, you really have to admit them for rasburicase and fluids and all of those things. Now, most people don't really need to get admitted somewhere along the line, but if you're not looking, you have no way of knowing. This is the importance of doing this ramp up and doing it correctly. So, she gets admitted for intensive management and does well and does the rest of her ramp-up without an issue.

So, what is the role of transplant in CLL in the age of novel agents in terms of timing and toxicity, where does CAR T fit in? In my mind, before we had all these new drugs, it was much easier to have these transplant conversations because we knew we did not have these layer upon layer of treatment options, so I think it is a very different discussion now that we have where patients can be on these drugs for years at a time. I think we are doing transplant much later in patients, but there are still lots of folks who make it to one of these treatment options.

DR. SHADMAN It's difficult because you don't know. I think there is a general agreement, that even if your patient is high risk, as long as they are responding to their first-line treatment, you just let them go with that first line. That should be a BTK inhibitor – ibrutinib, today. As soon as they go on the second line, that's the point where you don't have a very reliable third line. PI3 kinase inhibitors do not do very well in double-refractory patients. Here is the key – do we wait until patients fail venetoclax and then refer them for a transplant consult at least? Or should you do it when they are still responding? I think you should do it when they are still responding because finding a donor may take time, CAR T is not approved, you have to find a trial, you may need to fix their creatinine and you may need a couple of months to do that. You still need to have a reliable treatment option in your back pocket and that's venetoclax. If you know it still works, at least you know that if the patient goes through CAR T and if it doesn't work, you can put them back on venetoclax. We actually have a study at ASH showing in patients who fail CAR T and if they had failed both ibrutinib

and venetoclax, they had a very poor survival post–CAR T, so I think that is, again, in the absence of data, that is probably the most reasonable practice consistent with the guidelines.

MS. GOODRICH It was much easier when we didn't have all these good drugs. It's another good problem to have. So, in conclusion, hopefully you've realized all these novel agents have really improved the outcomes for patients with CLL. Side effect management is key. We do have more drugs than ever, but abandoning a class of drug is still very important not to do in these patients. Patient education again, we are sending folks out with a pill and relying on them to take that pill and really, it's all of you in the room that are the glue that holds all of these things together and keeps those balls in the air to have the best outcomes for patients.

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