SEQUENCING THERAPIES IN INDOLENT LYMPHOMAS (FL AND CLL)

Lisa Nodzon, PhD, ARNP, AOCNP®, Moffitt Cancer Center
Philip Thompson, MB, BS, University of Texas MD Anderson Cancer Center

INTRODUCER Welcome back everyone. I hope you enjoyed the Keynote presentation and had a nice break. For those of you who were in the Keynote, I hope you had some Kleenex. Our final presentation of the day in this room is sequencing therapies in indolent lymphomas. Please join me in welcoming Dr. Lisa Nodzon of the Moffitt Cancer Center and Dr. Philip Thompson of MD Anderson Cancer Center.

DR. THOMPSON Thank you so much for this opportunity to be here in this beautiful place. My colleague Lisa and I have the unenviable task of covering the entire sequencing of treatment in CLL and follicular lymphoma in under an hour, so, I will do my best. Some of the objectives we have, to kind of understand how we best treat patients with 17p deletion, I will talk a little bit about some of the combination therapies that are now available, and maybe some that will be available shortly, and discuss some of the newer therapies in follicular lymphoma. These are my disclosures.

Moving into treatment of CLL, we have really seen an amazing number of new approved therapies in the last few years in CLL. We have had second-generation CD monoclonals. We have had ibrutinib, a BTK inhibitor. We have had PI3-kinase inhibitors and finally the BCL2 inhibitor venetoclax. We now have an opportunity to see how we can best combine these treatments to maximize responses for patients. Really, there are two key biological processes in CLL

which we can now target with our new drugs. The first is B-cell receptor signaling. CLL cells live mostly within lymph nodes and they divide and grow mostly within lymph nodes. They get signals through the B-cell receptor from other cells and from soluble mediators within the microenvironment of the lymph node. Then you see a number of signaling molecules that transduce signals to growth and division of these cells. The key ones that have been targeted are BTK and PI3-kinase delta. We now have very effective targeted therapies that target those processes. The second key thing is CLL dramatically over expresses a protein called BCL2, which stabilizes the mitochondrial membrane and therefore prevents apoptosis. Venetoclax is a highly specific inhibitor of BCL2, which leads to fairly dramatic cell death.

The current first-line treatment of CLL revolves around either chemoimmunotherapy or monotherapy with ibrutinib. Those are the approved therapies that we have. I have listed the chemoimmunotherapy options in order of intensity from FCR, which is the most potent regimen, but tolerated only by younger and fitter patients, through to chlorambucil plus CD20 antibody combinations there. What do we really want from an ideal first-line treatment in CLL? I think we want to see high rates of complete remission. Ideally what we want to achieve is undetectable minimal residual disease. Minimal residual disease is when we look with a more sensitive technique than just morphology and can we see very small numbers of the cells remaining. The less MRD you have, essentially, the longer your progression-free survival is going to be. We want to see treatment with limited duration. Patients do not want to take therapy

forever, and if you have to take therapy forever, your risk of toxicity increases. Finally, I think we want treatment that is tolerable and effective in all patients, including older patients and those with comorbidity and those with unfavorable genomic characteristics like 17p deletion. You can see here that we don't really see all of these characteristics from either of our frontline treatment paradigms at this time. Ibrutinib rarely achieves complete remissions and undetectable MRD. FCR in contrast, while it can achieve a high rate of MRD negativity, the treatment is poorly tolerated by older patients and patients with comorbid medical conditions.

The assessment of patient fitness is crucial in terms of deciding on a first line of treatment paradigm. I emphasize patient fitness, rather than patient age, because age is not the best determinate of how well a patient will tolerate therapy. For example, the cumulative illness rating score has been used most commonly in clinical trials to determine whether a patient is eligible for a certain type of therapy. Those with a score of less than 6, and adequate renal function, a GFR less than 70, are generally considered fit for intensive regimens, such as FCR. Just looking at the chemoimmunotherapy briefly by means of background, FCR is a potent regimen with a high rate of undetectable MRD. It was the first regimen to demonstrate an improved overall survival in CLL. Bendamustine and rituximab, which is very frequently used in the frontline setting, was compared directly to FCR by the German study group CLL10 study. What it showed was overall there was an inferior progression-free survival for the BR regimen compared to FCR and there was no evidence of a plateau emerging on the

progression-free survival curve. However, for the subgroup of patients over 65 years old, there was significantly less toxicity for bendamustine and rituximab with a similar progression-free survival in that age group. It certainly is reasonable to continue to use BR in the older patients, rather than FCR. Chlorambucil and obinutuzumab was tested in the CLL11 study compared to chlorambucil monotherapy and that was in a group of older and unfit patients. It showed a markedly improved progression-free survival relative to chlorambucil alone. Similarly chlorambucil and ofatumumab was shown to have an improved PFS relative to chlorambucil, in actually both of those studies in improved survival. This is data from CLL10; again just confirming that overall FCR had a superior progression-free survival compared to BR, but again no progression-free survival seen yet in the patients over 65.

This is the data that I think is the most exciting data about FCR. What you can see here is this plateau emerging on the progression-free survival curve, when you get out to very long-term follow-up. This is the original FCR300 study from MD Anderson, and you can see that most of the patients that are on this plateau are those who have a mutated IGHV. We have started incorporating the IGHV mutation status into a lot of our decision making in front line, because if you have a patient who has a mutated IGHV, you really have the opportunity potentially to cure them with your first line of therapy. When we go on to look at the impact of getting undetectable MRD, you see even a better progression-free survival for that top group in the blue. Those are the patients that have a mutated IGHV and have undetectable MRD after therapy. Really that's what we are

aiming for with our first line of treatment. However, the problem is this subset of patients that do spectacularly well with FCR is relatively small.

This is data here from the German CLL8 study group, long-term follow-up on the left, and on the right is an Italian retrospective analysis. What you are going to see, again the group of patients with mutated IGHV are doing well, but if you look at the data on the right, they really only represent about less than a third of the patients, with a majority of the patients actually having this intermediate prognosis. Those are the ones with an unmutated IGHV or an 11q deletion. Also, what you can see here is the dismal outcome in the red curve, which are the patients with 17p deletion. They have a median progression-free survival of only just over a year, and this has been shown in multiple studies of FCR. Really, what we are starting to do at our center is say, okay, if you are going to be on that blue curve, then maybe chemoimmunotherapy is still reasonable. If you are on the yellow curve, then maybe we need to start looking at alternatives. If you are on that red curve with 17p deletion, then chemoimmunotherapy is inappropriate and we need to be using alternative novel agents. The other thing that is important to stress is: it is not just about 17p deletion. We need to look at *TP53* mutations as well. Most patients who have a 17p deletion will also have a *TP53* mutation. However, there is another group of patients who don't have deletion of 17p, who have a mutation in the *TP53* gene. They have similarly dismal outcomes as shown here. You may not be able to see very well, but in that right hand Kaplan-Meier curve, the patients in the red curve are those who only have a subclonal *TP53* mutation, so not all the cells have a *TP53* mutation,

but just some. What they have found is if you give chemoimmunotherapy to these patients, they will inevitably relapse, and what will happen is that *TP53*-mutated clone will grow out at relapse and become the predominant clone. We need to be looking for this before we treat patients and those who have a *TP53* mutation shouldn't receive chemoimmunotherapy.

What other options do we have for patients with 17p deletions? This is data from a phase 2 study that was done with ibrutinib, a Bruton's tyrosine kinase inhibitor in relapsed/refractory patients who have 17p deletion. Although we are not seeing a plateau on the progression-free survival curve, we still are seeing continuous relapses. This is a dramatic advance on what we had before. We have a medial progression-free survival of 2 and a half years. Compare that to frontline patients who always have better outcomes than relapsed/refractory patients, who have only around a 1 year progression-free survival after FCR. This has become the standard of care for treating patients who have either a 17p deletion or a *TP53* mutation in the first-line setting. In subsequent lines of treatment we have other options, which I will come to. Chlorambucil and obinutuzumab, this is the regimen that has been approved for older and unfit patients. The CLL11 study included patients who had a median age of 73, and they all had a high comorbidity index, or impaired renal function. You can see it had a significant advantage in progression-free survival compared to rituximab and chlorambucil, and compared to chlorambucil alone. It had a survival advantage compared to chlorambucil alone. This became an option for older

patients. Similarly, chlorambucil plus ofatumumab was shown to be superior to chlorambucil monotherapy in this group of patients.

What about ibrutinib? This has now been approved for all patients with CLL and it was on the basis of the RESONATE-2 study, which I am showing you some of the longer-term follow-up data here. This study included older patients. It did not include a comorbidity assessment. It was purely based on age, but there was a very impressive 2-year progression-free survival of nearly 90%. If you compare that to the median progression-free survival of around 29 months with obinutuzumab and chlorambucil. What's also interesting is that when you look at patients who have an inferior outcome with chemoimmunotherapy, those with unmutated IGHV or those with 11q deletion, it made no difference to their outcome when they received ibrutinib on this therapy, whether they had those features or not.

Based on all this data, this is one way of looking at first-line treatment for CLL and this is outside of clinical trials. This is essentially how we think about first line of treatment at our center. The first question is does the patient have 17p deletion or *TP53* mutation. If they do, and there are no contraindications, we would recommend ibrutinib therapy. Next, if they don't have these mutations, the question is, are they fit to receive FCR type therapy. If yes, then we go on to look at what their other FISH characteristics are and their IGHV mutation status is. If they are IGHV mutated, and they don't have 11q deletion, then we think chemoimmunotherapy is appropriate for a patient like that, and we prefer FCR unless a patient is over 65 just because of the superior progression-free survival,

as well as the fact that we have never seen a plateau on the progression-free survival curve and potential cures from BR. If a patient has unmutated IGHV or 11q deletion, we tend to offer ibrutinib for those patients based on the data from RESONATE-2 that suggests there is no inferior outcome if you are unmutated or 11q deleted with ibrutinib.

There are some key ongoing studies in first line of treatment of CLL which could potentially change these paradigms that I've just talked to you about. There are two ongoing studies comparing FCR to ibrutinib, plus rituximab. It will be very interesting to see both the overall results from those studies, but also whether subgroups of patients, such as those with mutated IGHV, have better outcomes with ibrutinib-based therapy. CLL13 is an intriguing study that compares three different venetoclax-based regimens to either FCR or BR and could potentially bring venetoclax-based treatment into the frontline for all patients. Looking at the older and unfit patients, there are several ongoing studies that I think are important. One is the Elevate CLL study, which may see the approval of acalabrutinib. The ILLUMINATE study recently announced that it met its primary endpoint, which is going to show that ibrutinib plus obinutuzumab is superior to obinutuzumab and chlorambucil. Whether the combination with obinutuzumab is superior to ibrutinib, however, we don’t know. CLL14 also made an announcement recently that it has met its primary endpoint, so this will show that venetoclax and obinutuzumab is superior to obinutuzumab and chlorambucil. We are now going to have the option of using venetoclax-based treatment frontline, rather than obinutuzumab. Finally, there is a study ongoing, the UNITY study,

which is looking to obtain frontline approval for umbralisib, which is a next-generation PI3-kinase inhibitor. As I was mentioning, potential first-line approvals in the near future: ibrutinib/rituximab, ibrutinib/obinutuzumab, acalabrutinib-based therapy, venetoclax-based therapy, and PI3-kinase–based therapy. We are going to have a huge array of options for patients, which may make treatment choices in some ways more difficult.

What about relapsed/refractory CLL? We have four approved agents in three classes which are targeted therapies: BTK inhibitors, PI3-kinase inhibitors, and BCL2 inhibitors. There is absolutely no head-to-head data on which order to use these drugs. There is data to show that a patient who previously had idelalisib or ibrutinib, that venetoclax works after failure of those agents, but we don't have data to show the reverse. The study that led to the approval of ibrutinib was the RESONATE-1 study that compared ibrutinib to ofatumumab, and you don't need statistics to see that there is a superior progression-free survival there. The long-term data from the phase 2 study have now shown a pretty impressive median progression-free survival in a very heavily pretreated population of 51 months, or more than 4 years. Interestingly, it is 43 months in patients with unmutated IGHV, which compares pretty well to what you see in the first-line therapy with patients with unmutated IGHV, which is why we are tending to now recommend ibrutinib-based therapy for those patients. You can see there was a small treatment-naive cohort in this study, and you can see very impressive long-term progression-free survival in the frontline setting for those patients.

Idelalisib and rituximab is approved in relapsed/refractory CLL, so idelalisib is a PI3-kinase delta inhibitor. You can see again this was a heavily treated population. The toxicity management, which Lisa will go into in detail, is a little more complex than with BCL2 inhibitors and BTK inhibitors and that's some of the reason that the progression-free survival curve appears to be dropping a little bit quicker than you see with ibrutinib because a number of patients have to stop therapy. Another PI3-kinase inhibitor was approved recently based on the similar study, compared against ofatumumab, so this is duvelisib, very similar progression-free survival curve to what you see with idelalisib.

Venetoclax was obviously first tested in patients with relapsed/refractory CLL. This drug has some unique toxicities, which Lisa will discuss, but it is very effective, again, in patients with 17p deletion and it has now been tested in a less heavily treated population, so patients who are only first relapse CLL and in combination with rituximab. You can see it is dramatically superior to bendamustine and rituximab in patients at first relapse. One thing that I really like about venetoclax-based regimens is that with venetoclax plus rituximab, you have a high rate of undetectable minimal residual disease. Sixty-two percent of patients in this study with relapsed CLL had undetectable MRD after therapy. Venetoclax is now approved for relapsed/refractory CLL regardless of 17p deletion, so it was initially approved on the basis of this study that I showed you previously in 17p deletion as monotherapy, but we can now use venetoclax plus rituximab rather than venetoclax monotherapy. It is difficult to compare results from study to study. These results look better than the initial venetoclax

monotherapy study, but you have to remember that patients on the initial study were very heavily pretreated and often had multiple lines of therapy. They were selected to have high-risk genomic characteristics. We cannot directly compare. That having been said, the toxicities are not significantly higher with combination therapy, and that very high rate of undetectable MRD gives us the potential to treat patients for a limited period rather than giving therapy indefinitely. I think that's a major advantage.

Finally, looking at patients who failed ibrutinib and idelalisib, this is an increasingly difficult group of patients that we are going to see more of. Before, we had venetoclax to treat patients who had failed ibrutinib. The median survival for patients after progression on ibrutinib was about 3 months. This study significantly improved the outcome for these patients. You can see a median progression-free survival now out to 2 years. There is a very high response rate of around 80%.

Now that we have got all of these different treatments available, which treatment should we give to patients with relapsed CLL? It's going to depend a lot on what they have had first. If they have had chemoimmunotherapy as first line of treatment, you have your choice of these novel agents. However, if they have had ibrutinib as frontline therapy, then that's a different situation where you probably will want to use a venetoclax-based treatment at first relapse. Essentially, no randomized data. This is a recent publication from a multicenter retrospective analysis that basically looked at the progression-free survival according to which kinase inhibitor you received first, was it ibrutinib or was it

idelalisib. You can see that the progression-free survival was superior for ibrutinib. I think, as I said, in part this is due to the better toxicity profile of ibrutinib. There isn't, however, any comparative data for ibrutinib versus venetoclax, or venetoclax plus rituximab. I think this is just a way that I think about the approach to treating relapsed/refractory CLL. If you are naive for both BTK and BCL2 inhibitors, you can use either ibrutinib or venetoclax plus or minus rituximab. If you intolerant or refractory to a BTK inhibitor, I use a venetoclax-based treatment. You could use idelalisib plus rituximab or duvelisib also in this situation. If you have venetoclax-refractory disease, there is limited data, and generally I think a clinical trial is the best approach for these patients, but it's worth a trial of ibrutinib. Patients who are refractory to both a BTK inhibitor and venetoclax are a very difficult group to treat and should really be treated with clinical trials. We are often trying to get these patients onto CAR T-cell studies. Finally, I will say if you are refractory to a BTK inhibitor or venetoclax, these are high-risk patients. If they are young and otherwise eligible, we are referring them for consideration of an allogeneic stem cell transplant, which we generally perform after we have given some salvage therapy, because the best time to do it is when they are responding to a treatment.

I will pass on to Lisa now to talk about some of the toxicities and management of these toxicities in CLL.

DR. NODZON Thank you Dr. Thompson. We will move into elaborating further on the targeted agents that he spoke about and particularly looking at the management of these toxicities, but the key just being to recognize

them, then moving into their management. Ofatumumab was the first fully humanized anti-CD20 monoclonal antibody. As you can see here, there are several FDA-approved indications dating back to 2009, but more so recently here in 2014, it kind of made its resurgence, based upon the results of the COMPLIMENT-1 trial that Dr. Thompson talked about, and particularly looking at those CLL patients that were unfit. The way it works is it will bind to the small and the large extracellular portions of the CD20 molecule that is present on the surface of B cells—even those B cells that have dim CD20 expression, which is the hallmark with patients with CLL. As such that it's a monoclonal antibody, it will bring about cell lysis. Cell lysis occurs through the mechanisms of complement-dependent cytotoxicity, as well as antibody-dependent cytotoxicity. Being that it is an anti-CD20 monoclonal antibody, we have to watch out for two black box warnings, that of hepatitis B reactivation. So, all patients prior to therapy should have hepatitis studies performed, and then during therapy if there is any suspicion for reactivation or even infection, just retesting the patient. Because we are further suppressing the immune system, watching out for progressive multifocal leukoencephalopathy, which is rare; however, patients presenting with any neurologic symptoms, just maintaining that in your differential. It carries a very high mortality rate. Obinutuzumab is another anti-CD20 monoclonal antibody. It has greater antibody-dependent cytotoxicity than does rituximab based upon the glycoengineering of the molecule itself. It is only approved to be given in the frontline setting based upon the results of the CLL11 trial, which was approved back in 2013. As Dr. Thompson was talking about, we

are now utilizing these monoclonal agents in combination with a lot of the novel targeted agents that are approved currently in the clinical trials. Again, the black box warning is the same for ofatumumab. There are some toxicities that we need to be paying attention to when patients are being treated with a monoclonal. Most importantly, tumor lysis syndrome; this is a big topic in hematology and this is due to the rapid cellular destruction that can occur when these monoclonals are being fused into a patient. You have to remember CLL patients can have bulky lymphadenopathy, they can have very high white blood cell counts, sometimes into the hundreds of thousands, so based upon that rapid cell lysis, you can get electrolyte disturbances that can have clinical consequences from renal failure to seizures, as well as to arrhythmias. Infusion-related reactions are quite common, grade 3 or higher are slightly higher in obinutuzumab at 21% to 31% as compared to ofatumumab. Again, based upon disease burden. We like to tell the patients if we can get you through day 1 of obinutuzumab, it might be smooth sailing from then on out, but our infusion center really has us on their cell phone dial whenever we are giving one of those agents. Hypotension, another hallmark of an infusion-related reaction, so again, just educating the patients to hold their antihypertensive medications on the days of the infusion. They can bring the medication with them, but to hold because if you run into hypotension, we don't want any other medications on board that may interfere with our management. As well, they can get rigors and fevers. For the patients with preexisting pulmonary or cardiac underlying conditions, they should be monitored a little more closely because hypoxia plus bronchospasms can occur. Most institutions

have their own premedication protocol, usually consisting of acetaminophen, as well as an antihistamine. Steroid dosing can be across the board. Some places follow package insert. We like to tailor it to the patient. Is this a patient with high disease burden? We might give a higher steroid dose. Is this a patient that has had a prior infusion-related reaction? But if you are going to start giving the higher-dose steroids, you might need to prophylax the patient as well against PCP, if not fungal infections. Neutropenia, grade 3 or higher, can also occur in around 26% of these patients. Sometimes you need growth factor or antimicrobials to support them through. Again, because we are further suppressing the immune system, just paying attention to bacterial and fungal pneumonias, as well as infections can occur. The reactivation of viral infections, we will prophylax all of our patients receiving an anti-CD20 against zoster. They will get an antiviral medication there.

As Dr. Thompson talked about, we have four oral targeted agents on the market for CLL that just really came about in the past 4 years, so the market continues to grow. It kind of feels like it's becoming the myeloma world as we start stacking things on top of each other. It will eventually be complicated like those regimens. Ibrutinib, as he mentioned, inhibits BTK, a protein important for B-cell survival. It has broad approval from the frontline to the relapse setting regardless of 17p. Idelalisib and duvelisib are two PI3-kinase inhibitors. Those are given in the relapse setting. Idelalisib given with rituximab and then venetoclax, also given in the relapse setting, now regardless of deletion 17p status. Ibrutinib has been designed to bind covalently to the kinase portion of

BTK, and again BTK is an important protein for B-cell survival, as well as proliferation, migration, and adhesion. It binds to the cysteine residue 481. That position is important when we start talking about patients that are resistant to ibrutinib with known resistance in that particular amino acid. Initially there is a half-life of around 4 to 6 hours, and then with steady state dosing, you get 24-hour inhibition. Because it promotes cell death through the mechanisms I just described, one of the greatest benefits patients receive when they start on ibrutinib, particularly if they have symptomatic lymphadenopathy, is a regression of that lymphadenopathy that can occur in a matter of just days. One thing that is very important to point out to the patient is that we expect to see an increase in proliferative lymphocytosis, just because we are blocking migration. Patients get very concerned and start to fear that they are progressing, but they are not. It's a mechanistic effect of the drug, just the redistribution of those lymphocytes, allowing them to be targeted, as well as adhering to their particular niche. We tend not to see true tumor lysis in these patients; however, you can see hyperuricemia. The lymphocyte count may rise for a while. Eventually it will plateau and then it could start coming down. The lymphocyte count may not normalize until a period of several months, if not by a year in some patients. Paying attention to uric acid levels is important. Some patients can also have flares of gout. As I mentioned earlier, for patients that are progressing, you should go ahead and test them through next-generation sequencing looking for mutations in BTK, as well as PLC-gamma-2. As such, there are clinical trials now

actually looking at patients with BTK resistance with one trial looking at vecabrutinib.

An integrated analysis was done looking at special adverse events of interest across the RESONATE and RESONATE-2 clinical trials. Those are depicted here and to the table on the right. These are patients that had a median time of exposure on ibrutinib of around 29 months, with a follow-up at 47 months. You can see about 30% of patients during the first year had discontinued ibrutinib due to adverse effects, and about 12% of those patients had dose reductions. Most of these events, as you see, are low grade. The key to them is just recognizing them early and providing good supportive care or other interventions that may be necessary. We will not talk about the diarrhea or arthralgias in detail, but again just note that they are low grade. The diarrhea tends to be self-limiting. You may see it more frequently in the beginning. Antimotility agents, or good supportive care with hydration, can be effective. The arthralgias can become problematic in our patients that have underlying rheumatologic disorders, which some patients with CLL in fact do. The arthralgias can therefore be complicated and the fact that as you are going to see, just due to the risk of ibrutinib with bleeding, we are not recommending NSAIDs for these patients. That's why I am saying it can be a little bit problematic to manage those arthralgias if the patients have debilitating symptoms from them. We often dose reduce to manage that.

Hypertension, bleeding, and atrial fibrillation – we are going to dive into a little bit deeper, just because of the clinical consequences that can occur in our patient population. But again, just noting that most of these events are low grade,

the key is recognition and early intervention. As I just mentioned, ibrutinib can be associated with bleeding, while ibrutinib has been designed to bind to the kinase portion of BTK, we have to remember, in the molecular biology world we like to say there is conservation of confirmation. So, BTK is a member of the tech kinases. There are off-target effects from ibrutinib, and those off-target effects are what you see when you see these adverse events. In the little cartoon on the right, you can see for simplicity, BTK and the tech kinases play key roles in glycoprotein IV signaling, that's necessary for collagen-mediated platelet aggregation. Therein lays one of the mechanisms responsible for why we see patients with increased amounts of bruising, or even petechiae or prolonged bleeding. This impact is partially reversible after about 2 and a half days of holding ibrutinib and fully reversible within 1 week. That data there alone tells us, when patients ask us, I have to go for an elective surgery, how long do I need to hold ibrutinib? For the minor surgeries, we say 3 days, for the major surgeries and that perioperative period, we say 7 days. Atrial fibrillation is something else to be paying attention to. Around 11% of patients can experience this. This risk is going to be present all throughout the therapy course. Due to these off-target effects, if the BTK and tech kinases are important members to regulate a pathway PI3-kinase and AKT, which is a critical regulator of atrial rhythm under stress. When you are thinking about the body under stress, CLL patients are prone to pneumonias, so maybe a higher risk of atrial fibrillation in that setting. Perhaps they have a history of atrial fibrillation, so a higher risk there, or even with uncontrolled hypertension. Standard rate and rhythm management is

recommended and just paying attention to avoidance of the CYP3A4 inhibitors during that time period. Atrial fibrillation is not a reason to discontinue ibrutinib. Things can become challenging and dicey, however, in our patients that have symptomatic atrial fibrillation. Is this a patient that may need a cardioversion or a patient that may need an ablation, because now we are starting to talk about having to add to their regimen one of these direct oral anticoagulants. It may be wise, and it is something that we do at our center. We are fortunate to have a cardio-oncologist on staff that is very well versed in these agents that we can partner with to help manage these patients. If not, the recommendation is to also partner with a cardiologist to help manage these patients, because things can become a little bit dicey at that point. Nonetheless, we recommend using a systems-based scoring system of does this patient really need to be on an anticoagulant? Vitamin K antagonists are not recommended. These patients were excluded from the original clinical trial, so we have very limited safety data on their use. We do caution and educate our patients at every clinic visit against other agents that may cause excessive bleeding. And again, here comes the direct oral anticoagulants, the concept being that they do increase the risk for bleeding on our patients. If you think about the kind of patient population we are treating, they are higher risk in that sense. Some patients come into ibrutinib already being on one of these oral anticoagulants. Perhaps that is a good time to reassess does this patient further need to be on that agent or is this a patient that now needs to be placed on one of these agents because we have run into an

issue perhaps with atrial fibrillation? Again, just partnering with a cardiologist will become really important during this time period.

We talked about the surgery. I do want to mention one other very common one that we see all the time in practice is patients that go for a colonoscopy. We advise them also to hold ibrutinib around this time period as well, because if polyps are found, they are going to be excised out. They aren't going to go back to do that. We have had patients present with GI bleeding. We just warn all the patients to hold it in advance. The same thing when you go to see the dermatologist because they are always getting something clipped off. For any patient presenting with serious bleeding-related events, even though their platelet count is normal, the only way to reverse the effect of ibrutinib is to transfuse platelets. Some patients will wear a medical alert ID bracelet or they will carry a list of their medications in their wallet in the event of emergency, so the emergency response personnel know what drug they are on.

Hypertension is something that needs to be aggressively managed in these patients. The incidence of grade 3 or higher, in about a quarter of them, increases with time. Again, we have to counsel our patients to monitor their blood pressure from home. Again standard management, but watching out for those concomitant medications that may interact. In addition to monitoring themselves from home, again we have to educate for these patients to have a very controlled blood pressure. If you need to partner with a cardiologist on that, it is advised, because again, uncontrolled hypertension can increase the risk for atrial fibrillation, but more importantly cerebral hemorrhaging.

Idelalisib is the first PI3-kinase inhibitor that was on the market. It targets the delta isoform that's unique to leukocytes. PI3-K does play an important role in inhibition or regulation of T regulatory cells. Therefore, patients on this agent may have an increased risk for these immune-mediated toxicities. The original frontline trials were halted just due to the increased risk for infections in these patients, so it is not recommended to give this agent to any patient who is treatment naive or an untreated CLL or SLL patient. Black box warnings are listed here. Again, we are starting to see these rather as a class effect across the board for PI3K inhibitors. Just to be aware of them, there can be hepatotoxicity, diarrhea or colitis, pneumonitis, as well as infections, and on the trial, I believe there was an issue with one patient with intestinal perforation.

Select adverse events are shown here based on the results of the 116 study that was experienced in greater than 20% of these patients. I just highlighted by the red stars the ones that we are going to talk about today, the ones that are the most problematic and the ones you will have to manage in practice. If we just look at the grade 3 or higher, for those that received idelalisib, we see diarrhea/colitis at 5%. We are going to tease these two out in a minute. Pneumonia risk around 8% in these patients. Pneumonitis, something else to be on the alert for at 4%. Transaminitis at around 8%. Neutropenia can occur in around 37% of these patients as well, so thinking about, do they need growth factor, or perhaps be placed on a prophylactic antimicrobial? The key to management with the diarrhea is to first just exclude that it is due to an infection. These patients are immunosuppressed as a consequence of their disease, they

are in the relapse setting, so the first thing we do is rule out that it is not due to an infection. The next thing we have to ask ourselves is what is the onset time? Because that is going to give you the clue. If it is an early onset diarrhea, it typically occurs around 2 months, it's usually your run-of-the-mill diarrhea, grade 1 or grade 2. These patients can be managed with supportive care, as well as antimotility agents and very close monitoring. If it is a later onset diarrhea, if the patient is beginning to experience loose stools around 8 months, if not a period longer than that, it's typically grade 3 or higher. These patients may experience as well electrolyte disturbances, and they are usually hospitalized if it is not caught early enough. This diarrhea tends to be characteristic of an immune-mediated colitis. Important to note, that while patients are receiving idelalisib all throughout their therapy, they need to be monitored for CMV reactivation. In cases of CMV colitis, there might not be viral titers present in the peripheral blood. These patients may need to undergo a colonoscopy with biopsy to prove that it is due to CMV because that's going to affect your management with an antiviral. Nonetheless for patients with colitis, recommendation is to hold the drug and then treat them with steroids. The steroids can be enteric, PO, or IV. The initial study that was done with budesonide, which is an enteric steroid that some of you may be familiar with, initial studies showed that patients treated with budesonide had a mean time to resolution of around 12 days as compared to those that did not. It took them about a month to resolve. But again, the patients do get better with time, but they are going to require a lot of aggressive supportive care to get them through. Again, just thinking about the kind of

patients that we see with CLL. If patients are willing to be rechallenged, we rechallenge them with a smaller dose. Sixty-seven percent of the patients in the trials were rechallenged, and about half of them without recurrence. If it is a patient with CMV reactivation, in that sense, the monitoring is therefore going to go monthly thereafter.

Pneumonitis versus pneumonia sometimes can be a little hard to distinguish. Pneumonitis is relatively a rare event; around 4% of the patients experience that. Patients can present with differential pulmonary symptoms. They might have a nonproductive cough. They might be very short of breath. It can happen very acutely, very quickly, versus over the course of a few days. On all of our patients that are on a PI3-kinase, the minute they come through the clinic we make sure we get a pulse ox on all of those patients. If you are thinking the concern may be for pneumonitis, they do need a good CT of the chest. We like to call down to the radiologist and tell them what we are looking for. Sometimes pneumonitis can be difficult to distinguish, or the radiologist may not know specifically what you are looking for. Some patients will require a bronchoscopy with bronchoalveolar lavage as well. If your suspicion is pneumonitis, you hold the drug. Median time to onset, it can happen any time that first year, but we have seen it even later than that. So again, patients coming in with pulmonary complaints, just keeping that in your differential. The management for it, again, permanently discontinue idelalisib altogether. These patients may require long courses of steroids as well. Often they have a pulmonologist, as well assisting you with that, for a very slow steroid taper on

them. The patients can go down rather quickly, so as soon as you start hearing complaints like this, or through the phone triage, those patients need to be brought in for evaluation.

Pneumonia grade 3 or higher, around 8% of the patients. Again, they've got underlying CLL, so they are immunosuppressed, but now we have them on a therapy that's going to suppress them even more. As we know, pneumonia is an inflammation or infection of the lung. We often have to do bronchoscopies in our CLL patients. They could have had an underlying infection for a long period of time, or something atypical showing up. Pneumocystis can occur while patients are on this PI3-kinase inhibitor. In the idelalisib clinical trial, it was not something that was known, so PCP prophylaxis was not mandated during that time point. From there forward, with all of the PI3Ks and under clinical trial, PCP prophylaxis is mandated in those trials. It is now part of the NCCN guidelines as well for those patients.

Hepatotoxicity typically occurs in the first 3 months while patients are on idelalisib. We do have to caution our patients as well to avoid hepatotoxic agents. The two biggest culprits being acetaminophen as well as alcohol. It is managed with dosing interruption until it resolves to grade 1. Around three-fourths of the patients were successfully rechallenged. And again, monitoring out for viral reactivation because, again idelalisib is given with rituximab.

Duvelisib, the newest comer to the market approved about 4 weeks or so ago, is a dual inhibitor of both the delta and gamma kinases. On your left is a cartoon showing the inhibition of delta, but on the right, that gamma piece, what it

is showing is that the gamma isoform is involved in recruitment, as well as differentiation of cells in that microenvironment that are supporting the B-cell survival. It also serves the immunosuppression as well. Black box warning, across the board for the PI3-kinases, some select adverse events are shown here again. No new safety signals with what we say compared to idelalisib, except here in the DUO study, diarrhea and colitis were teased out, because after we learned from the first experience they knew what to look for. So, colitis grade 3 or higher can occur in around 12% of these patients. Again, the same timing story holds true when you are looking for these potential toxicities.

Venetoclax – this one is unique in the sense that it binds to BCL2. BCL2 is a protein that is overexpressed in several hematologic malignancies. Particularly in the case of CLL, which makes these lymphocytes look like they have these very long eternal life cycles, because BCL2 will sequester away these proteins that are involved in cell death. When venetoclax binds to BCL2, it will sequester it away. Those proapoptotic proteins are then free to go about and do their job function and initiate the caspase cascade and bring about cell death. This occurs independent of the TP53 pathway, but just the mechanism alone is why you see the tumor lysis. It has two FDA-approved indications, both in the relapse setting, regardless of 17p. The biggest contraindication is during that 5-week ramp up period, to avoid any strong CYP3A inhibitors. Before venetoclax was on the market, back when it was called ABT-199, that ramp up period was over the course of about 3 weeks or so, and with that shorter ramp up period, they actually saw more cases of tumor lysis syndrome that had clinical consequences.

The ramp up period now is over the course of 5 weeks, but it really must be strictly adhered to. Special adverse events of interest – we know patients with CLL can, just on their own, develop autoimmune hemolytic anemias. However, as a monotherapy, it was seen in around 7% of these patients. Myelosuppression is something to watch out for, grade 3 or higher neutropenia is around 64%. Again, the patients may require growth factors to support them through. GI disturbances, diarrhea, and nausea around 40%. Those tend to be self-limiting as well. The diarrhea can be managed with antimotility agents. You tend to see it, if you are going to see it, during the initial ramp up period. Nausea as well can be there. Most patients that we see that develop this again don't require an antiemetic, but it seems to be when they go from the 200 to the 400 mg dosing if you are going to see it. They do take it with food and water, it is recommended. Also, recommended to take with a low-fat meal. Higher-fat meals can increase the absorption of venetoclax. Infection, we see it across the board, just because they have CLL, but the risk for pneumonia grade 3 at 9%. Then grade 3 or higher laboratory evidence of tumor lysis syndrome is around 3 to 6%. The key to the tumor lysis risk is profiling the patient from the get go. On the bottom right is a cartoon showing that 5-week ramp up. Those first 4 weeks, that particular dosing goes for 7 days straight. It is recommended that they do not skip any of the doses; that they actually complete each ramp up as indicated. I won't go through this in detail. It's very nicely laid out in the package insert. All patients need to have a CT prior to the start of therapy. You need to know those lymph node sizes. Then, of course, we have the lymphocyte count and the peripheral blood.

Based on those two factors alone, you can place your patient into low, medium, or high risk. Low and medium, you can treat them outpatient. All the high-risk patients are admitted for the day 1, as well as the day 8 dosing, and then, as you can see, there are some post-dosing labs that will come along with that day 1 and day 8. The big key there with giving venetoclax is just sitting the patient down and having them understand that for those first 5 weeks, they are very committed to coming into your office during that time point.

In summary, infusion-related reactions, they are manageable events, but they are inherent to ofatumumab and obinutuzumab as a mechanism of their job function. Patients receiving ibrutinib should be counseled, as well as monitored closely for bleeding-related events, as well as cardiac-related events. You may need to refer them to a cardiologist to assist you. All patients receiving idelalisib need to be counseled on the diarrhea, as well as the infection risk on when to report. Venetoclax has a very favorable risk/benefit profile, but the key to giving that drug is patient profiling before you start, that 5-week ramp up course. Then, because we are seeing so many oral oncolytics that continue to come out on the market across the oncology world, and these drugs come from specialty pharmacies, the patient needs to maintain an accurate medication profile with whatever pharmacy they may be using. We see it very commonly in clinical practice; they come in and there is a new medication on board, but because we are talking about some pretty life-threatening events with patients here, the interaction checks need to be performed.

Next, we will move into the treatment of follicular lymphoma.

DR. THOMPSON Follicular lymphoma is a little bit different from CLL. They are both indolent lymphomas, but the treatment remains significantly different. One of the major points of difference is that we really haven't seen quite the same explosion of novel therapies in follicular lymphoma. In particular, in the first-line setting, we still have chemoimmunotherapy as the basis of treatment. Just a little initial map for how to manage frontline treatment of follicular lymphoma. There is a small group of patients that present with localized disease, stage I to II. Those patients are potentially curable with radiotherapy, but radiotherapy has some toxicity, so we generally only give that to people if we think they are going to live at least 15 years. Most patients, however, present with advanced-stage disease. If they are symptomatic they can be safely observed, similar to what we do with the watch-and-wait phase of CLL. If they are symptomatic, we can treat them with chemoimmunotherapy and that's usually with RCHOP, CVP, or bendamustine. Subsequently there is a decision to be made about whether or not to give rituximab maintenance. The reason for the watch-and-wait for a subgroup of asymptomatic patients with follicular lymphoma is that there has never been a survival benefit shown for early treatment of patients. This is, again, like CLL, an incurable disease theoretically. We wait for them to fulfill what we call the GELF criteria usually to start treatment. This is based on bulky lymphadenopathy, systemic symptoms, very large spleen particularly if it is causing compression of the stomach and patients are unable to eat. If they have pleural or peritoneal effusions or if they have a significant circulating disease, and then finally if they have cytopenias.

What about the choice of chemoimmunotherapy? This is still a little bit controversial. There was a noninferiority study, called the StiL study, which compared bendamustine/rituximab to RCHOP, and that included both a number of histologies including follicular lymphoma. It showed a superior progression-free survival for bendamustine compared to RCHOP, including when the just analyzed the follicular lymphoma patients. Additionally, the bendamustine/rituximab had a lower rate of myelosuppression, lower infection rate. It doesn't cause peripheral neuropathy, and it didn't cause hair loss, so there were some advantages to the bendamustine/rituximab therapy. Why do we not do BR for everybody? Well, one of the problems is that there was a dramatic improvement in outcomes for patients who received rituximab maintenance after RCHOP. We don't really know whether that same benefit is achieved after bendamustine/rituximab. Additionally, there is another study that I will talk about called the GALLIUM study, which compared rituximab and chemotherapy to obinutuzumab and chemotherapy. That actually showed a higher rate of fatal adverse events in older patients receiving bendamustine, in both the rituximab- and the obinutuzumab-containing arms. Really, either of those treatments remains a reasonable choice. Generally though, for very elderly patients and patients with comorbidities, you would look at a less intensive regimen like ICVP or even rituximab monotherapy.

This is the GALLIUM study, a comparison of R chemo to G chemo, and then maintenance treatment for 2 years for both of them. These are the progression-free survival results. This was a plenary session at ASH in 2016.

Overall, a superior progression-free survival for the obinutuzumab treatment arm. That held true regardless of what chemotherapy regimen, as you can see here. The obinutuzumab-treated arm was associated with a higher rate of infusion-related reactions, higher rate of febrile neutropenia, and there was a higher cumulative incidence of grade 3 for infection, and I will stress there is no overall survival benefit for this. Progression within 24 years, this POD24, is something you will hear a lot in follicular lymphoma. This is an important milestone because essentially if you receive, say RCHOP, and you progress within 24 months, your prognosis is extremely poor. They looked at what was the incidence of POD24 according to treatment arm in the GALLIUM study and it was significantly lower in the group who received obinutuzumab. When choosing the monoclonal antibody, rituximab is essentially less toxic, it has lower cost, and later I will show you that if you become rituximab refractory, you may be able to be salvaged with obinutuzumab. Whereas with obinutuzumab, it is a more potent drug, there are more patients who get undetectable MRD, and it does have a superior progression-free survival, as well as that reduction in POD24. Again, either may remain the reasonable choice.

This is the PRIMA study, which was the major study which led to this concept of rituximab maintenance in follicular lymphoma, so again patients received initial chemoimmunotherapy, rituximab chemoimmunotherapy, and then 2 years of rituximab maintenance afterwards. You can see significant improvement in progression-free survival, and actually a 10-year follow-up was presented at ASH last year and it remains a highly significant difference between

the two treatment arms. However, there is still no overall survival benefit even when you follow patients out to 10 years. In a separate study, they looked at the risk of transformation to diffuse large B-cell lymphoma, and the compared patients who did and did not receive rituximab maintenance, and there was a small absolute risk reduction for transformation at 10 years in those patients who received maintenance rituximab. When we are deciding on whether or not to give maintenance rituximab, several things to consider: 1) What chemotherapy did they get? We don't know if it's beneficial after bendamustine/rituximab. 2) How well did they tolerate induction? There is this very small reduction in the risk of histologic transformation, which is obviously a desirable thing, but again important to stress no survival benefit from rituximab maintenance.

So, what about relapsed/refractory follicular lymphoma? Again, this is the data that shows that progression or death within 24 months. You can see if you progress within 2 years of RCHOP, which is the redline, your outcome is very poor overall. This is the group of patients we really need to be particularly focused on ways we can improve outcome. This is a complex slide, and I am indebted to my colleague for providing this slide. The way we think about these patients, first of all, do they need treatment? There may be the opportunity to do surveillance. If they need treatment the next thing is are they in this high-risk group where they progressed within 24 months? If they are not, then essentially they get another round of chemoimmunotherapy. That's chosen essentially based on the patient, their characteristics, and what they received before. If they don't respond to a second round of chemoimmunotherapy, then we need to be

considering clinical trials or one of the novel agents I will discuss later. If they were a poor prognosis patient, and progressed within 24 months, these are the type of patients where we may look to do an autologous transplant if they have a chemo-sensitive relapse.

This is the GADOLIN study. This was a group of patients who were rituximab refractory and other poor prognosis group of patients with follicular lymphoma. They were randomized to receive either bendamustine along or bendamustine with obinutuzumab and then obinutuzumab maintenance. This study showed a significant progression-free survival benefit for the obinutuzumab arm. This is definitely an option for patients who have failed rituximab-based therapy.

The other group of agents that have been approved in follicular lymphoma are the PI3-kinase inhibitors. Unlike CLL we have not seen a significant benefit from BTK inhibitors, or BCL2 inhibitors, which was surprising given that BCL2 is dramatically overexpressed in follicular lymphoma as a result of hallmark chromosomal translocation. The PI3-kinase delta inhibitors in contrast have shown benefit in follicular lymphoma. This is the study that led to the approval of idelalisib. You can see from this waterfall plot, that more than half of the patients achieved a partial response. These are patients who are refractory to two lines of therapy and a relatively low rate of complete remission. They have a progression-free survival benefit of under a year, but one thing that was interesting was that the progression-free survival after idelalisib was actually better than the progression-free survival from their previous therapy. Copanlisib

is a dual inhibitor of PI3-kinase alpha and delta, and similarly to idelalisib, it was tested in patients who had failed at least two lines of therapy and showed a similar progression-free survival result. Finally, duvelisib, which is a PI3-kinase delta and gamma inhibitor, and is also approved in CLL, has been tested in that same high-risk group of patients with an overall response rate of just under 50% in follicular lymphoma and progression-free survival of around 8 months. You can see compared to, say, venetoclax and rituximab in CLL, or ibrutinib in CLL, we are really having relatively short progression-free survival in follicular lymphoma of around a year, once we are down to our second relapse. So, definitely still some work to be done.

To summarize, approximately 20% of patients relapsed within 2 years and are refractory to therapy, resulting in a 5-year overall survival of less than 50%. The really high-risk patients are the ones who relapse within 2 years after rituximab and alkylating agents. They have limited treatment options, and we need clinical trials for these patients. As I mentioned, there is very limited efficacy for BCL2 inhibitors or BTK inhibitors, unlike CLL, so novel therapies in follicular lymphoma are needed, for example CAR T cells. Finally, I will hand back to Lisa to discuss the AEs of some of these drugs.

DR. NODZON Our final slide is looking at adverse events of interest in copanlisib. We won't discuss the other ones for duvelisib and idelalisib, because they are roughly similar, but copanlisib is the dual inhibitor of both alpha and delta, so you will get the same toxicities with the delta isoform. What's new here is the toxicity attributable to the alpha isoform, and that in particular is the

hyperglycemia, as well as the hypertension. These tend to be transient, but because the drug is given once a week, 3 weeks on, 1 week off, these patients need to have controlled blood pressures, as well as be controlled in terms of their glucose levels, so maybe not an agent of choice for an uncontrolled diabetic or a patient with uncontrolled hypertension. The hyperglycemia tends to be transient, grade 3 incidence or higher is 41%. More so 5 to 8 hours post the infusion of the drug, but also can last up to 24 hours after the drug. So, again, the patient needs to have a controlled blood glucose level prior to administration of this drug. Then again, with the hypertension grade 3 or higher, in around a quarter of these patients. So, again, blood pressure needs to be controlled. The other signals that we see down there, the transaminitis, as well as the neutropenia and lung infections, similar across the board to what we saw for the other PI3-kinase inhibitors. But, these two particular side effects that I just brought up now are something to pay attention to in the patient in terms of profiling the patient, maybe if you are thinking that they may or may not be adequate here. As I promised that was the last slide.

DR. THOMPSON Do we have time for questions? I didn't think so.

DR. NODZON I thought we were doing good on time.

INTRODUCER In the interest of time if maybe people have questions, if you don't mind staying for a few minutes afterwards. That way we can let those go that have meetings to get to. I want to thank both of our speakers for a wonderful presentation. Thank you.

Just to remind everybody. This was a Smartie presentation, so if you are one of our Smartie participants, you will be getting an email. Please look at that and answer promptly.

Thank you all so much for joining us today.

[END]