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Individualized Approaches in CLL/SLL: Meeting the Needs of Your Patients Now and Preparing for the Future

Announcer:
Welcome to CME on ReachMD. This replay of a live broadcast is titled “Individualized Approaches in CLL and SLL: Meeting the Needs of Your Patients Now and Preparing for the Future,” is provided by Prova Education. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Lipsky:
Hi, I’m Dr. Andrew Lipsky from Columbia University in New York, and I’d like to welcome you to the program, “Individualized Approaches in CLL/SLL: Meeting the Needs of Your Patients Now and Preparing for the Future.” And with that, I’ll introduce the overall program. So, I’ll begin with a brief presentation about continuous therapy in frontline CLL/SLL, focusing on the BTK inhibitors. Then, my colleague from Mass General, Dr. Jake Soumerai, will give a presentation focusing on time-limited frontline therapy in CLL/SLL. After that, Dr. Catherine Coombs from UCI Health will give a presentation on selecting and sequencing therapy for relapsed/refractory CLL. And in the last portion of the program, we’ll have some discussion – first a case-based discussion about selecting initial therapy, then a panel discussion about the future directions for the field, and we’ll conclude the program.

So, beginning with some brief remarks about continuous therapy in frontline CLL focusing on the Bruton’s tyrosine kinase inhibitors, it’s been known for some time that CLL cells are addicted to activation of the B cell receptor pathway, and that by targeting BTK, a critical kinase in proximal B cell receptor signaling, this small class of molecules inhibits cell proliferation and migration and decreases NF-κB activity, which leads to decreased cell survival. Shown here is data from the RESONATE-2 study, the frontline registration trial for ibrutinib, which led to its approval. This study was a randomized comparison of ibrutinib versus chlorambucil with the primary endpoint being progression-free survival. With up to 8 years of follow-up, the median PFS has still not been reached.

From the first major frontline trial to the present day, you can see on this slide the NCCN preferred regimens for treating first-line CLL. The second-generation BTK inhibitors, acalabrutinib and zanubrutinib, now both have a category 1 recommendation as first-line preferred regimens from the NCCN, and so does time-limited therapy with venetoclax, which Dr. Soumerai will discuss in detail. You can see that ibrutinib is also recommended, but it is not a preferred first-line regimen according to the NCCN.

Turning back to the more mature data for ibrutinib, you can see that there is now a PFS benefit in at least five randomized studies with an overall survival benefit in two. Highlighted here is one of those trial, the ECOG trial, in which ibrutinib was compared to the most active chemoimmunotherapy regimen. Previously untreated patients less than 70 years of age without deletion 17p were randomized to ibrutinib plus rituximab versus fludarabines, cyclophosphamide, and rituximab. The primary endpoint here is progression-free survival, and at 3 years of follow-up, the ibrutinib-rituximab treatment arm demonstrated an improved PFS compared to chemoimmunotherapy, and that translated into a statistically significant overall survival benefit with 98.8% of ibrutinib-treated patients alive at three years.

Another study was the phase 3 Alliance study comparing ibrutinib to chemoimmunotherapy in an older untreated CLL population via a three-arm randomization. 547 patients greater than or equal to 65 years old were randomized to receive either ibrutinib monotherapy, ibrutinib with six cycles of rituximab, or bendamustine and rituximab. With a median follow-up of 55 months, the median PFS was 44 months with BR and was not reached in either ibrutinib arm. The 48-month PFS estimate was 76% from both of the ibrutinib arms, and

at the latest follow-up, there remained no significant differences in overall survival across arms. Notably, no additional benefit was seen with the addition of rituximab to ibrutinib.

I'll now turn to the second-generation BTK inhibitors, which were developed to have more on-target kinome profile binding being more specific to the BTK kinase. We saw a PFS benefit for acalabrutinib over the chlorambucil comparative with the schema shown on the next slide in the ELEVATE-TN study. This phase 3 study enrolled 535 elderly or unfit CLL patients, and the drug was given either as monotherapy or in combination with obinutuzumab with chlorambucil-obinutuzumab as a comparator. On the right-hand panel, you can see the published PFS curves, and notably, this study was recently updated after four years of follow-up, at which point the median PFS was not reached in the acalabrutinib arms. And interestingly, even though obinutuzumab is only given for the first six months of therapy, the estimated PFS of 48 months was 87% for acalabrutinib plus obinutuzumab versus 78% for acalabrutinib alone and 25% for the comparator.

Of course, we also have zanubrutinib that's still pending approval in CLL but is approved in mantle cell lymphoma, and keep in mind that in CLL, zanubrutinib has a category 1 recommendation from the NCCN. This drug was evaluated in CLL in the SEQUOIA trial where it showed a PFS benefit over the BR comparator. Now in more detail, the first cohort of patients from this trial without 17p were randomized to receive either zanubrutinib 160 mg b.i.d. versus standard chemoimmunotherapy with bendamustine and rituximab. And on the right, we're looking at the primary endpoint, which was progression-free survival at about 2 years. This trial reported a significant PFS benefit for all zanubrutinib with a PFS hazard ratio of 0.42.

Now that we've reviewed data from 3 different BTK inhibitors, you might be wondering – do we have direct head-to-head comparisons of BTK inhibitors in CLL? And the answer is, yes, we do, but with the asterisk that the current randomized comparison data is really in the relapse/refractory setting and so that this data would need to be extrapolated to front-line. The first study I'll highlight here is the ELEVATE-RR trial, which is a randomized trial of acalabrutinib versus ibrutinib in relapsed CLL. This was designed as a noninferiority study, and note that these were all high-risk patients with either 11q deletion or deletion 17p, and that they were heavily pretreated, with 45% of patients in this study having deletion 17p. The primary endpoint was assessed by an independent review committee for noninferiority of PFS, and you can see here that the PFS curves are essentially overlapping. Since the way that the study was designed, the noninferiority endpoint was met. A secondary endpoint, the rate of A-fib and A-flutter, was assessed for superiority, and seeing here, you can see that the numbers for A-fib/A-flutter are 6% for acalabrutinib and 15% for ibrutinib, and this was statistically significant. And there are also differences in the rates of hypertension – 9% for acalabrutinib versus 23% for ibrutinib.

There is another randomized comparison head-to-head of BTK inhibitors, again in a relapsed setting. This was the ALPINE study, which compared zanubrutinib to ibrutinib, and we just saw updated data from this study at ASH in December with assessments this time made by an independent review committee. Here we saw a progression-free survival benefit at 29.6 months with a PFS of 79.5% in the zanubrutinib arm versus 67.3% in the ibrutinib arm, and notably, atrial fibrillation was also substantially reduced on zanubrutinib – seen in 5.2% of patients versus 13.3 on ibrutinib.

What about patients with TP53 aberrations? Here I mean deletion 17p or TP53 mutation. So, in contrast, and in lucky contrast to the chemoimmunotherapy hero, it's clear that with indefinite BTK inhibition strategies, patients with TP53 aberrations – again, this is about 5 to 7% of patients – are doing much better. These patients have PFS estimates with single-agent ibrutinib and calculated in a pooled analysis of 89 patients in four clinical trials, and with a median follow-up of 49.8 months, the median PFS has not been reached, and the PFS and OS estimates at four years were 79% and 88%, respectively. This slide is meant to show that TP53-aberrant patients have substantially improved outcomes regardless of the small-molecule therapy chosen, although the PFS may be less durable with time-limited therapy approaches for this patient subgroup, and Dr. Soumerai will focus on that in his presentation.

What about the side effect profile of covalent BTK inhibitors? We've already spoken a little bit about atrial fibrillation, but in the next few slides, I want to provide some management pearls for dealing with this BTK class effect-type side effects as well as what are termed the nuisance side effects – these include contusion, hypertension, arthralgia, and diarrhea – and though it's thought that all of the BTK inhibitors can cause any of these side effects, in the next few slides I'll highlight individual effects that may be seen preferentially with a particular agent. So, ibrutinib, for example, is known to cause myalgias and arthralgias and can also be associated with rash. What about acalabrutinib? Acalabrutinib has an idiosyncratic effect of having a headache. That headache is responsive to caffeine and usually only lasts for the first two or three weeks of therapy. What about zanubrutinib? Zanubrutinib has perhaps some idiosyncratic toxicities, particularly GI toxicity and maybe some cytopenias, although that remains to be under further investigation.

What about the management of particular BTK side effects? Well, starting with atrial fibrillation, a good strategy here is to screen every patient for cardiovascular risk factors before starting therapy. For patients with preexisting A-fib, this isn't an absolute contraindication to starting BTK inhibition, although it can be a bit more challenging, and I'd encourage you to have a conversation with the patient's cardiologist. Useful tools here can be the CHADS2-VASc score as well as beta blockade for treating A-fib, and when you do introduce

anticoagulation, such as apixaban, can be dose-modified, enoxaparin can be given concurrently, but one thing that should be never be given concurrently is a vitamin K antagonist. Do not put patients on a BTK inhibitor and warfarin.

What about the risk of bleeding? We know from the lab that BTK inhibitors do have effects on platelets, yet it's been encouraging that in several clinical trials we've seen the BTK inhibitors are only associated with minor bleeding and contusions, and they really do not portend a substantial and increased risk with major hemorrhage. That being said, you should counsel patients to avoid over-the-counter supplements that may exacerbate bleeding risks, such as vitamin E or fish oil, and it's recommended to hold BTK inhibitors for three days before and after minor procedures or longer for major procedures, and if someone does develop a major bleeding event on a BTK inhibitor, transfusing platelets, regardless of the platelet count, will help to reverse the aggregation defect and correct the bleeding dialysis.

What about these nuisance side effects? Hypertension can actually be quite prevalent, and we know that in the case of ibrutinib, the rate actually increases overtime, and patients are on lifelong therapy. Over 80% of patients have at least a 10-point bump in their systolic blood pressure, and more than 10% will have an increase of greater than 50 millimeters of mercury. A good strategy here is to work with the primary care physician to optimize the patient's blood pressure at baseline and continue to monitor throughout therapy.

What about diarrhea that's sometimes seen? Well, this can be managed conservatively with supportive care and antimotility agents. What about arthralgias? Arthralgias can be a tremendous pain for patients on BTK inhibitors, and one of the ways to mitigate this is to use dose holds or dose reductions for patients who have a grade 3 side effect that is impacting their activities of daily living.

So, what do we think about when starting initial therapy with a BTK inhibitor or selecting initial therapy in CLL? We really look at a confluence of factors. We look at the patient's comorbidities; we look at particular characteristics of their treatment, be it efficacy or side effect profile; and we look at characteristics of the patient's particular disease, for example, their TP53 aberration status.

So, to sum up, the long-term results of BTK inhibitor studies in the front-line continue to show excellent PFS outcomes with overall survival benefits in the select cases that I've mentioned, and these agents continue to produce favorable outcomes even for high-risk patients – patients who clearly would do worse with chemoimmunotherapy, patients with TP53 aberrations, and unmutated IGHV. There are some treatment-emergent adverse events that can be seen, but careful attention to detail and selecting the right drug for the right patient can help mitigate these effects. We do look forward to more mature data from BTKi comparisons that might inform us going forward when trying to select one BTK inhibitor over another, and with that comment, I'll conclude this portion of the presentation. Thank you for your attention.

Dr. Soumerai:
Thank you for the opportunity to present on time-limited treatment options in CLL. Time-limited therapy is not a new concept. Recall that before ibrutinib was approved for the initial therapy of patients with CLL, time-limited treatment was actually the norm. Patients would typically receive a 6-month course of chemoimmunotherapy, then would be observed off treatment for a period, and only treated in the relapse setting if they again met criteria for treatment. So, this history really underlies the significance of time-limited approaches to patients. Despite the approval of ibrutinib as initial therapy, many patients continue to opt for cytotoxic agents to avoid the chronic treatment of ibrutinib. So, time-limited therapy is clearly an important goal for our patients, and this really makes sense, right? It allows for treatment-free intervals, which may avoid chronic toxicities that are important to these patients.

So, can we overcome the greatest drawbacks associated with drugs like ibrutinib, i.e., that it is continuous therapy, it's administered until a progression or intolerance, and associated with chronic toxicities and avoid cytotoxic chemoimmunotherapy altogether, i.e., just get rid of this and use all novel agents? The BH3-mimetic venetoclax is approved in CLL, and combinations of venetoclax and anti-CD20 monoclonal antibodies are the only time-limited targeted therapy regimens currently approved in this disease. In the first-line setting, venetoclax is administered for 12 months in combination with obinutuzumab. In the relapse setting, it's administered for 24 months in combination with rituximab. And so with these approvals, there's really no longer a compelling argument, in my opinion, to use cytotoxic chemoimmunotherapy in CLL.

Venetoclax-containing regimens have not been compared directly to BTK inhibitors in any prospective studies that have been reported. So, what data really informs the decision supporting these regimens? So, venetoclax and obinutuzumab was approved for the treatment of previously untreated patients with CLL on the basis of the CLL14 trial. Now, this was a randomized phase 3 trial in which treatment of CLL patients who required therapy but had significant comorbidities were randomized at 12 months of venetoclax and 6 months of obinutuzumab or to 12 months of chlorambucil and 6 months of obinutuzumab. The primary endpoint was investigator-assessed PFS. Baseline characteristics are shown here and were typical with about 60% of patients exhibiting an unmutated IGHV status, 12% with a p53 mutation or deletion, and appeared similar across treatment arms. Venetoclax-obinutuzumab was associated with a statistically significant and clinically meaningful improvement in progression-free survival as shown here with a hazard ratio of 0.31. Importantly, there was no difference in overall survival in this analysis.

So, how does VO fare across key risk groups? As with other targeted therapy studies, the PFS benefit appears to be driven by those with IGHV-unmutated CLL. Although TP53 aberrancy appeared to impact PFS in both groups, recall that only 12% of patients exhibited a TP53 mutation or deletion, and so this subgroup analysis is clearly underpowered. So, I had to exercise some caution when drawing any sort of conclusions based on this p53 subgroup analysis.

MRD outcomes data are depicted here for the CLL14 trial, and in the peripheral blood, 76% of patients achieved undetectable MRD at 10 to the minus 4, 42% at 10 to the minus 6. In the bone marrow, 57% of patients achieved uMRD at 10 to the minus 4. We do see recurrent detectable MRD in the months following treatment discontinuation, although most patients remain undetectable for some time, and clinical remissions are quite durable as well.

So, why does MRD matter? That VO achieves such a high rate of uMRD is important and really sets this therapy aside from BTK inhibitors, which do not eradicate MRD when given as monotherapy typically, and from chemoimmunotherapy, which achieved uMRD less frequently than venetoclax-obinutuzumab does. There's increasing data showing that MRD response is associated with PFS outcomes as depicted here with uMRD at 10 to the minus 4 being associated with survival outcomes, and there's actually a more recent data suggesting even additional benefit with even deeper MRD levels down to, for example, 10 to the minus 5 in a recent analysis.

So, what are the key takeaways from these data? VO is superior to chemoimmunotherapy for progression-free survival in unfit, previously untreated patients with CLL and achieves frequent uMRD, which we know is associated with survival outcomes. But can these data be extrapolated to fit patients? What about patients with p53 aberrancy? Also, how do we manage the toxicities that we know to be associated with venetoclax-based therapies?

Hematologic toxicities are very common among patients with CLL receiving venetoclax-based therapies with grade 3/4 neutropenia occurring in 53% of patients in the VO CLL14 trial. A primary driver for this is the fact that, in CLL, bone marrow burden is typically quite high, and this also underlies the importance of maintaining early-dose intensity. You know, for patients where CLL is driving much of the immunologic toxicities, we want to try to drive down the CLL bone marrow burden in order to allow patients to subsequently tolerate treatment even better over time, and so for this reason, for patients with grade 3 or worse neutropenia and the absence of fever or infection, I typically continue venetoclax at full dosing with growth factor support as needed. If neutropenia persists despite growth factor support or the severe neutropenia occurs later in a patient without significant residual CLL, these are the patients where I consider dose reductions as per the product label.

TLS can occur with venetoclax and requires a 5-week ramp-up schedule to gradually debulk tumor, decrease TLS risk, but really TLS is a very rare event with appropriate TLS risk identification, prophylaxis, and monitoring. Key here is TLS risk assessment, and the major distinction is whether a patient is high risk – this means that they require hospitalization for inpatient monitoring for a night during weeks 1 and week 2 of the ramp-up – or low or medium risk in which case outpatient monitoring is typically appropriate. How do we identify patients who are high risk? These patients have either a 10 cm or greater lymph node or a 5 cm or greater lymph node plus a 25,000 or greater lymphocyte count. All patients require uric acid lowering therapy and hydration throughout the ramp-up, and there are subtle differences between risk groups as shown here.

There are many drug interactions associated with venetoclax, including CYP3A inhibitors or inducers, P-gp inhibitors. Really important that we look at the med list and consult our pharmacists if there are any significant interactions which might warrant either a treatment change to one of their concurrent medications or a change in the venetoclax dosing, as this can be a little complicated during the venetoclax ramp-up. However, it is extremely rare that this prevents me from actually using a venetoclax-based therapy. It just requires some thinking in advance and requires the patients to let me know of any new medications while they're taking their venetoclax.

This slide is just highlighting a number of different studies which are looking at combinations of BTK inhibitors with venetoclax with or without obinutuzumab and demonstrate that we're seeing high efficacy with very high rates of uMRD with these regimens. However, whether these regimens result in improved efficacy compared with venetoclax-obinutuzumab alone, saving the BTK inhibitor for the relapse setting, is really unknown. However, these data are clearly very encouraging.

So, can we treat young, fit patients with CLL with venetoclax-obinutuzumab? This is a really important unanswered question from CLL14. CLL13 is a randomized trial of chemoimmunotherapy with FCR for those under 65 and BR for older patients versus VR versus VO versus VO plus ibrutinib, or IVO or GIVe as just to, as here, described. In each of the venetoclax-containing arms, venetoclax was given for 12 cycles. Ibrutinib was continued in the GIVe arm for 12 cycles and permitted for up to 36 cycles if MRD was still detectable. Here are the MRD outcomes at month 15. Notably, VR did not result in an improved uMRD rate compared with chemoimmunotherapy. However, the VO and IVO regimens were each associated with highly significant improvements in peripheral blood uMRD when compared with chemoimmunotherapy. In data not shown here, the addition of ibrutinib, however, resulted in more febrile neutropenia and infections and clearly adds toxicity to VO, and this analysis was not powered to compare the MRD rates between VO and IVO, and so these data between the toxicity and the lack of a demonstrated benefit of the addition of ibrutinib do not support the addition of

ibrutinib to VO at this time.

In conclusion, venetoclax plus a CD20 antibody is a time-limited regimen with venetoclax administered for 12 months with 6 cycles of obinutuzumab in the first-line setting. VO is associated with high rates of uMRD, and responses appear quite durable. Combinations of BTK inhibitors with venetoclax with or without a CD20 antibody also appear highly effective but require additional data – additional comparative data – to determine whether these really add benefit without increased unacceptable toxicity when compared with a doublet. I look forward to your questions during the Q&A. Thank you very much.

Dr. Coombs:
Hi, my name is Catherine Coombs, and I'm happy to be able to speak about selecting and sequencing therapy for relapsed and refractory CLL and SLL. So, in the relapsed setting, we have two main treatment approaches that have demonstrated efficacy in this setting, including BTK inhibitors and venetoclax, which can be used with or without anti-CD20 antibodies. So, there are important considerations for selecting relapsed/refractory therapies for our patients. The first, of course, is what did the patient receive in the front-line setting? But then, what were their toxicities from that therapy, and what was their response to that therapy? One should always consider the patient's age and comorbidities, which may have changed between the relapsed/refractory setting to when they were treated in the front line. Next is their current disease status, which can include their cytogenetic markers, molecular testing for TP53 mutations, imaging, and bone marrow biopsy, which is especially important in the setting of any unexplained cytopenias. Lastly, one should always consider the patient's social determinants of health as well.

The current NCCN guidelines suggest that both BTK inhibitors and venetoclax-based regimens are the preferred options for relapsed/refractory CLL and SLL. This includes patients who are both older and younger with comorbidities or without comorbidities, and they're always preferred regardless of the presence or absence of del(17p) or TP53 mutations. So, what we see is that acalabrutinib, abrutinib, and zanubrutinib are listed as potential treatment options for the BTK inhibitor class, and then venetoclax with rituximab is listed as well.

So, why is planning for sequential therapy so important? Well, what we know from this study that pooled four different prospective trials of ibrutinib is that patients often discontinue ibrutinib for a variety of reasons. Transformation can occur, it's typically an early event, however, disease progression is known to occur, especially over multiple years on therapy. However, the most common reason for discontinuation when using a BTK inhibitor in the front-line setting is other events, which primarily relates to intolerance. Ibrutinib resistance, however, is an important consideration when we're thinking of progressive disease, and what we know is that the acquisition of BTK C481 mutations is the most common mechanism of resistance. However, patients can also have PLC gamma 2 mutations or, in 20% of the cases, no such events can be identified.

So, I mentioned that an intolerance is the most common reason for ibrutinib discontinuation. Well, what are our options? There is very nice data from Kerry Rogers and collaborators looking at the use of acalabrutinib in the setting of prior ibrutinib intolerance, and this study demonstrated that that can be a very effective approach to gain control of the disease and enjoy a progression-free survival period.

Do these toxicities recur? Well, the good answer from this trial is mostly no, and so the majority of ibrutinib-intolerance events that led to patients being enrolled on this study did not recur. However, of the ones that did recur, the majority of time events recurred at a lower grade.

We now have head-to-head data on ibrutinib with acalabrutinib. This is the ELEVATE-RR trial. This enrolled patients with relapsed and refractory CLL and SLL. Patients had a median of two prior therapies, and they were enrolled if they had del(17p) or del(11q). It was designed as a noninferiority trial, and, in fact, both agents had a similar median progression-free survival of 38.4 months, but we got a really good look into the head-to-head toxicity comparison where we see lower rates of both any-grade atrial fibrillation and any-grade hypertension for the acalabrutinib-treated patients compared to the ibrutinib-treated patients. These rare ventricular arrhythmias have previously been reported with ibrutinib. They did not occur in the ELEVATE-RR trial. However, there has subsequently been data from the Ohio State University group demonstrating that acalabrutinib can lead to ventricular arrhythmias. However, their definition of ventricular arrhythmias included both V-tach/VFib but also symptomatic PVCs, which may have influenced the total VA incidence rate in that study.

We also have data looking at the newer-generation BTK inhibitor zanubrutinib in the setting of previous BTKi-inhibitor intolerance. This study primarily included patients with prior ibrutinib intolerance. However, there were a few acalabrutinib-intolerant patients, and what we see from this study is that this is also an effective strategy where the majority of BTKi-intolerant events did not recur upon treatment with zanubrutinib.

We recently got a presentation and publication in the New England Journal of Medicine looking at the final analysis of the ALPINE study,

which was the head-to-head comparison of ibrutinib with zanubrutinib. This study enrolled all comers from a cytogenetic standpoint and was also a relapsed/refractory trial. However, the median prior lines of therapy in this study was 1. What we see from the progression-free survival curves is that zanubrutinib led to a superior progression-free survival compared to ibrutinib both in the intention-to-treat population but also when looking at the subset of patients with del(17p) or TP53 mutation or both. When we look at the head-to-head comparison of toxicity, atrial fibrillation and flutter, of course, is a huge concern when using BTK inhibitors as a class, and zanubrutinib led to a lower rate of any-grade A-fib and flutter as compared to ibrutinib – specifically, 5% compared to 13%. There was no difference, however, in the rates of hypertension between these two agents.

Venetoclax is a BCL-2 inhibitor that we have also seen excellent efficacy in the relapsed and refractory setting. This study specifically focused on patients who were ibrutinib refractory or ibrutinib intolerant and used venetoclax as a continuous monotherapy. This was a very high-risk population in that patients had a median of four prior lines of therapy, and almost half had del(17p). What we see is a median progression-free survival of around 2 years.

The more modern way of utilizing venetoclax is time-limited therapy, and the MURANO trial examined the use of venetoclax combined with rituximab over two years compared to bendamustine and rituximab administered over a standard six cycles. The MURANO trial demonstrated a superior progression-free survival for patients that were treated with VenR compared to BR, and it also demonstrated an overall survival benefit. The MURANO trial looked at patients who relapsed and required a subsequent therapy, and what this demonstrates is that using a BTKi after progression on VenR is a highly active approach with an overall response rate of 100%. This is particularly important because the MURANO trial primarily enrolled patients post-chemoimmunotherapy, and so these patients were typically BTKi naïve, and so it's good to know that changing the sequence of therapy using a BTKi after venetoclax also is an effective approach.

We also have real-world data examining the post-venetoclax use of BTKi, which is effective in BTKi-naïve patients based on these real-world data by Anthony Mato and collaborators. The curve on the right, however, demonstrates that reusing a BTKi inhibitor after venetoclax and after BTKi that had been used in the past is not an effective approach if the prior BTKi was discontinued due to CLL progression with a median PFS of around 4 months. This brings me to the mechanisms of resistance once again, and so we know that ibrutinib resistance is via the acquisition of C481S mutations. Unfortunately, acalabrutinib and zanubrutinib share this mechanism of resistance, and so it is important to note that BTI resistance that contributes to disease progression diminishes the efficacy of all covalent BTK inhibitors.

So, a few takeaway messages from this presentation are that TKIs are very effective in relapsed/refractory CLL and SLL, and BTKi intolerance does not exclude the use of a newer-generation BTK inhibitor, such as acala or zanu. However, BTKi resistance does require changing to a different class of drugs with venetoclax being the most well studied, though there are a number of agents in development that also show promise. Lastly, there is an increasing data to support the activity for BTK inhibitors in venetoclax-refractory CLL.

Here is my summary for relapsed and refractory CLL and SLL. We always have to ask the question – is there an indication for treatment present? If there is, the selection of therapy in the relapsed setting depends on what they received in the front-line setting. Patients with prior BTKi and progression, I definitely would consider a venetoclax-based approach. Patients with prior venetoclax, I would consider a BTKi as the next approach. In patients who were treated with prior chemoimmunotherapy, both BTKi's and venetoclax are acceptable approaches in the relapsed setting. With that, I would like to thank you for your attention, and I look forward to the Q&A session.

Dr. Lipsky:
Hi. I'm Dr. Andrew Lipsky again from Columbia University in New York, and it's a pleasure to welcome you now to the live portion of our program. I'm joined once again by my colleagues, Dr. Soumerai and Dr. Coombs, who are on the line, and for the next portion of the presentation, we'd like to start by a discussion of selecting initial therapy in CLL, and so to go over front-line cases, you remember from my part of the presentation, we talked about that really selection of initial therapy is related to a confluence of factors. Those include patient comorbidities, treatment characteristics, and disease characteristics, and maybe one of the best ways to go over the selection process is actually to do some cases. So, we prepared two cases for you today, and so I will start by talking about a first case, and I'll pull in my colleagues to ask some questions and respond as we go through.

So, for the first case, we have a 72-year-old with progressive CLL – so, a 72-year-old woman who had been on observation for 2 years. She has comorbidities, which are significant for hyperthyroidism, hypertension, and paroxysmal atrial fibrillation, and at her follow-up visit, we see that her absolute lymphocyte count has increased from 30,000 to 126,000 within 3 months. She also has lymphadenopathy of the neck which has increased in size, which is making her socially uncomfortable. People are noticing this at work. She has grapefruit-size nodes in her axilla, and she's also newly anemic for the first time. Her hemoglobin has dropped to slightly less than 10, and she lives two and a half hours away from the clinic and is driven to the visit by her granddaughter. So, that was a lot of

factors for the case. So, one of the questions maybe I'll open up to my colleagues. Dr. Soumerai, from what I've said so far in this patient, does the clinical picture look like it warrants treatment? And, you know, which factors so far may favor indefinite or time-limited therapy? And what other prognostic factors might we look at?

Dr. Soumerai:
Thank you. You know, when thinking about treatment initiation in CLL, we always think about what are the key indications for treatment? The iwCLL guidelines really inform this decision, and for this patient I think there are really a number of things that would push me towards considering treatment. For example, development of anemia, she appears to have a rapid lymphocyte doubling with a 3-month increase from 32,000 to 126,000. Let me just point out that oftentimes when folks have a single point in time when we see a rapid increase, I often like to repeat this and make sure that it's not from some other factor – for example, an infection, a vaccine, something that could be driving this – but I think that the whole story here of this progressive lymphadenopathy, rapid lymphocyte – lymphocyte doubling and some anemia would push me towards initiating treatment. Thinking about, what would favor indefinite therapy, I think the distance from the hospital makes time-limited treatment, which requires a number of visits for infusions and medical acts ramp-up, would push me a little bit towards a BTK inhibitor-based approach and the prognostic factors, I would want to know the IGHV status, I'd want to – but really the most important thing here is p53 status, and so the FISH studies as well as next-gen sequencing for p53 are really critical and would help guide the decision of which treatment we should be pursuing.

Dr. Lipsky:
Excellent, excellent. So, let's advance the case forward then a little bit based on that request, and let's say that the patient's prognostic studies are already sent, and we already knew from the baseline stated that the patient was IGHV unmutated, but now at this point we do repeat prognostics, and we see that on FISH we see a deletion 17p, and also by next-generation sequencing, we see a TP53 mutation. So, Dr. Coombs, you know, would those particular prognostic studies influence your treatment decision about selecting initial therapy?

Dr. Coombs:
Absolutely. So, you know, I think we found from her clinical presentation that there were already some factors that were making us lean towards a continuous BTKi, and her prognostic factors further support that as likely the best approach in her case. So the presence of having a del(17p) and TP53 mutation – what that tells us is that her progression-free survival, should we consider her for a venetoclax-obinutuzumab regimen in the front-line setting, is likely going to be on the shorter end and so what we know from the CLL14 trial is that patients with TP53 and 17p aberrations had the shortest progression-free survival out of any prognostic subgroup, and that was around 49 months. So, not to say that there's not some benefit – this is way better than what we were seeing back in the chemoimmunotherapy days – so, I don't think it's the wrong thing to discuss that with the patient, but I think because of these other barriers that we've already discussed specifically her distance to the center that maybe that wouldn't be the best approach. What we know from long-term studies of BTK inhibitors is that continuous suppression of the underlying CLL clone through use of a BTK inhibitor can lead to much longer progression-free survival. Now, of course, we don't have head-to-head data yet, but it looks like that's more on the order of six, seven, you know, maybe even eight years in some patients, and so that does appear to be a very good option for this patient.

Dr. Lipsky:
Excellent, and I absolutely agree with everything you said, and I think in the interest of time, I'll just round out, you know, this case presentation by saying that seeing someone with preexisting atrial fibrillation – for example, if that patient was on anticoagulation to begin with – that's something you'd want to address with the cardiologist, and that is not an absolute contraindication. The presence of apixaban, say, is not a contraindication in combination with a BTK inhibitor. As I mentioned in the presentation, you know, rarely we do see some patients on Coumadin – that would be – but for someone on apixaban, there are strategies you could do. You could, you know, counsel patients to avoid other things that may interfere with anticoagulation. Sometimes we do a slight dose reduction of apixaban, and I often do that in my practice, but that wouldn't preclude this patient from receiving therapy, especially given the high-risk genetic factors. So, with that being said, I think now we can move on to the second topic for discussion, which is really the future directions for CLL, and so, we saw a lot of emerging data at the ASH meeting with drugs that have not yet been approved in CLL, but it's reasonable to speculate that in the near term, sequencing patients in the relapsed/refractory setting we may see some drug approvals, and so one of those drugs was pirtobrutinib, and I think maybe, Dr. Coombs, if you could help us out by talking a little bit about that drug and some of the data we saw and where you see it fitting into the CLL treatment landscape.

Dr. Coombs:
Absolutely. So pirtobrutinib is a BTK inhibitor, but its primary difference between the BTK inhibitors that are already available on the market is that it's a reversible or noncovalent inhibitor, and so when we look at ibrutinib, acalabrutinib, zanubrutinib, those are covalent inhibitors. In order for them to have their optimal activity one needs a wild-type BTK protein with no mutations at the C481 residue. The most common mechanism of resistance to these drugs is through acquisition of mutations at that binding site to where they can no

longer effectively inhibit that target. Pirtobrutinib has a distinct binding mechanism through the ATP-binding pocket, which works whether or not that mutation is present or absent, and so it has been shown to have activity in patients who have progressed on prior covalent BTK inhibitors. There is a very large trial that's been previously presented – the phase 1/2 BRUIN trial – and at ASH we got an update to the data. It was like 700-some patients. Over 300 CLL/SLL patients were enrolled, and the good thing about the ASH presentation is we now have a lot longer follow-up and so with this further follow-up, we have two very nice findings. Number one is that we see that the overall response rate appears to increase with further time on the drug. So, earlier iterations of the study it was around a 60-some percent response rate. Now it's closer to 80% for the patients who are the toughest to treat, meaning those who have been failed by a prior covalent inhibitor and a prior BCL-2 inhibitor, but it's around 82% for the entire cohort of patients who had had a prior covalent BTK inhibitor. We've also now reached the median progression-free survival, which is just under 20 months for the entire cohort – median of three prior lines of therapy – and 16.8 months for that really tough-to-treat population who have had prior BCL-2 inhibitor, which is primarily venetoclax or – and prior covalent BTK inhibitor. In that subgroup, it's not just those two drugs – they had a median of five prior lines of therapy. The other really nice thing about pirtobrutinib is how well tolerated it is, and so even now with this longer degree of follow-up, we're seeing very low rates of high-grade AEs. The only event that occurred with any frequency was neutropenia, but that was still not that common – I think around 10% was deemed treatment-related – and the rates of discontinuation due to treatment-related AEs are very low. So, when you look at studies of covalent BTK inhibitors, ibrutinib – it's like 20%. Even now with longer follow-up the rate of discontinuation for pirto is around 2%.

Dr. Lipsky:
That was really an excellent summary of the data, Dr. Coombs. I appreciate that very much. Maybe a couple questions regarding pirtobrutinib: So, when you see a patient progressing on a BTK inhibitor, do you routinely send genetic studies for resistance mutations? And does that really matter for a patient who is progressing on a BTK inhibitor? Is that something that's going to influence your treatment? How do you see the role of that at clinical progression?

Dr. Coombs:
Yeah, you know, I have sent mutation testing and I know a lot of people do routinely, but I kind of don't anymore because it may be because of my own nature as a cost-conscious clinician, but I don't think it changes management in cases where a patient's very clearly progressing. Now, if, you know, sometimes there's gray situations – are they progressing or are they not? – where maybe, you know, the presence of a mutation would help me in a clinical decision, but, you know, otherwise I think if it's clear progression, whether they have a mutation or they don't, it's not going to change my next step, which is to change their therapy and not do another covalent BTK inhibitor. About 20% of patients don't have a C481 mutation or a PCL gamma 2 mutation, and so, I don't know, I think my own view is if it doesn't change your management, maybe it's not worth the cost of the test. Now, we sent it in the clinical trials – I don't think it's the wrong thing to send it to kind of get the full picture, but that's my own logic.

Dr. Lipsky:
Yeah. I actually more or less agree with that in my own practice. I think progression is progression, and it's nice to know that for the C481 mutants that they're super likely to have a response based on the mechanism of the drug, you know, but for patients progressing, they're progressing, and this seems to be a highly efficacious drug. Dr. Soumerai, do you generally agree with that? Or any differences in your practice?

Dr. Soumerai:
I do. I do generally send repeat sequencing at progression. I think that often this is largely academic although, you know, acquisition of a high-risk mutation like a p53 mutation at relapse does occasionally make me a little bit more inclined towards a continuous versus a time-limited option in the relapsed setting. So, it depends on the patient, it depends on what their baseline genetic risk factors are, and what the treatment options I might be considering to begin with.

Dr. Coombs:
Yeah, just to add to that point you know, at my own institution, it's a different panel to get the BTK-resistance mutations than TP53. I totally agree – I think it is helpful to know if they have had acquisition of a TP53 mutation, so that I do send on subsequent treatments, and if it's a young patient, it may point me more towards even considering aloe for these really refractory patients, so that's a good point.

Dr. Lipsky:
And then maybe the last question on pirtobrutinib, we have seen some data including a paper in the New England Journal of Medicine that describes the mechanisms of progression on pirtobrutinib. So, you know, do we see this drug as being potentially a helpful use in our armamentarium where patients are going to have prolonged remissions on the drug? Or, is it possible that there are mechanisms of escape for this one, too? How do you – if you had to speculate a little bit Dr. Coombs – how would you evaluate that possibility?

Dr. Coombs:

You know, I think with any targeted agent resistance happens – I don't know if that's ever not happened once we've had enough time to study these mechanisms, but I don't think that takes away from how much this could benefit patients once it's more widely available. And so the biggest area of unmet need is patients who have progressed on a prior covalent and prior venetoclax. There is almost nothing that leads to any meaningful progression-free survival. PI3K inhibitors chemoimmunotherapy – the PFS is like 4 or 5 months based on real-world studies, and so pirtobrutinib's 17 months in that subgroup – wow, that's way better than anything we have, but resistance is inevitable, and the resistance mechanisms are interesting, and so it was a small study – it was just 9 patients that they had pre and post samples on – but what it showed is that the majority of patients developed new BTK mutations that were distinct from the C481 binding site, and some of these lead to this kinase-dead BTK protein, and so I think it shows us a lot about what we could expect with sequencing, and there's some concern that may lead to cross-resistance to other covalent BTK inhibitors and so I think we need a lot more time to understand how the drug works if we're considering moving it to earlier lines of therapy, especially if we were to move it to prior to covalent inhibitors, but as it stands, I think it's a huge benefit in the post-covalent and post-venetoclax setting, but I think also it can be really valuable post-covalent for those patients that just have difficulty accessing venetoclax, whether it's due to long distance to a center that can do it, travel considerations, renal failure or, you know, dysfunction, etc.

Dr. Lipsky:
Excellent, and, yeah, I completely agree in highlighting, you know, the unmet need in that double-refractory BTKi and venetoclax-refractory patient population. This is a really exciting drug for that particular patient cohort. So, with that being said, I think we should move on to the audience questions portion. So, a bunch of audience questions have actually come in, and looking at them right now, I actually think there was a question for Dr. Coombs. If you can use a BTKi after venetoclax-rituximab and then after ibrutinib in refractory CLL, which do you choose first? Okay. So, I guess that's asking about – I'm not sure if that's asking about BTKi progression. Well, I may ask you that kind of question.

Dr. Coombs:
Yeah.

Dr. Lipsky:
So, if you have a patient progressing – BTKi inhibitor – a BTK inhibitor, you know and assuming pirtobrutinib is approved, you know, where would you see that fitting in, for example? How about that as a question?

Dr. Coombs:
Yeah, so to answer that question, I could see it very easily fitting post-covalent BTKi and post-ven, but I also, as I mentioned, could see it going before venetoclax given the ease of use and low toxicity profile. Venetoclax actually has a very favorable toxicity profile but, you know, the ramp-up necessity takes a lot of visits to and from. You know, my read of the question is, so you can do BTKi, then ven; you can do ven, then BTKi – which one do you choose? And to me, I think that really kind of is where considering the whole patient matters. So, I think they're both good options, but they're different, and so, I think that's where a shared decision-making can really help, talking to the patient about – gosh, is time-limited therapy that requires a bit more in the way of visits upfront more important to you, or would you rather have something a bit more simple but it is something that you have to stay on continuously – because I think either order is fine. They're just different, and so you know, they're complicated discussions with the patient, but I think both approaches are totally fine. The caveat is, when patients have TP53 or 17p-deleted CLL, we do seem to think – again, not comparative data but based on what we've seen in different studies – you'll probably get the longer PFS doing a continuous BTKi, but I still don't think it's wrong to do time-limited Ven-OB cause you still always have the option of re-challenge, and the patient still will get a time off therapy, but it's a shorter time to progression, and so that's just part of what education entails when talking about these options.

Dr. Lipsky:
Great. Thank you, Dr. Coombs, and that was definitely the right read of the question. Dr. Soumerai so there's a question about your approach to TLS mitigation and monitoring. So, how successful are these types of approaches? What should I tell my patients about their risks?

Dr. Soumerai:
This is such an important question, and I think that, first, these approaches are extremely successful. We know that if we properly assess TLS risk and then give them appropriate mitigation strategies like uric acid lowering therapies, oral plus/minus intravenous hydration based on the risk factors and appropriate monitoring that actually it's very uncommon that patients develop any laboratory or clinical tumor lysis syndrome that if it develops – in my practice, it's typically you know, often single laboratory abnormalities that may simply require some additional hydration and retesting, but this is actually relatively uncommon with appropriate mitigation strategies. And so, in telling patients about this, I present the TLS risk as more as a risk of burden rather than a risk of medical complications. It's simply that there's going to be a lot of visits and a lot of labs but that ultimately the risk of having clinical consequences related to the TLS is extremely low.

Dr. Lipsky:
Great, and there's a question here that maybe I'll address to myself. So, in the phase-3 Alliance study, adding R to I was no better than ibrutinib alone in terms of PFS. Are there patient disease-specific reasons where you might want to use an anti-CD20 therapy in treatment of CLL? So that's a good question. I would highlight in particular that there may be differences between the BTKi's with their combinations, and particularly we saw updated data from the ELEVATE-TN trial where acalabrutinib was combined with obinutuzumab, and, in that trial, we did see arms with Acala-O and Acala – it wasn't really adequately powered for that particular comparison, but if you look at the PFS curves there with the updated data, those curves certainly do come apart, and so that's one of the interesting questions I think in CLL going forward about the role of anti-CD20 therapy. In my patients, I do sometimes use an anti-CD20 therapy in combination with acalabrutinib when I give acalabrutinib. There are certain things that would influence my decision about that. If you look in that study, also, it was also underpowered to assess for 17p/TP53-aberrant patients – for whatever reason, there didn't appear to be a separation in that group, maybe because of the higher underlying mutational burden in TP53-aberrant patients, and the biology of the disease functions a little bit differently in that group – but I very often, I do often give it, and certainly there were considerations early in the pandemic about sequencing anti-CD20 therapy upfront. Another consideration would be we often have CLL patients that have autoimmune phenomenon and get treated with steroids and then eventually they don't respond, or they need CLL-directed therapy – that's another potential consideration – but I kind of tend to do that on a case-by-case basis, but no, I do not give rituximab with ibrutinib in my practice. I only do AO in certain select patients, and I think we need to see more data there.

Let's see – there are some additional questions right now. A question for Dr. Soumerai: In the relapse setting, do you always give time-limited therapy with venetoclax and an anti-CD20 antibody, or do you occasionally use venetoclax alone? And maybe I can tack onto that question. Which anti-CD20 therapy do you use?

Dr. Soumerai:
That's a great question. So, in the relapsed setting, I typically do use time-limited therapy with venetoclax anti-CD20 antibody. I often use obinutuzumab although acknowledging, that the data, the standard-of-care regimen that's really off-label – the standard-of-care regimen is venetoclax-rituximab in the relapsed setting with the venetoclax given for two years. In whom what I would consider venetoclax therapy – you know, I would say in particular those folks with a p53 mutation or deletion, and if I'm going to go down that route, I do not include the CD20 antibody. I just give the venetoclax as monotherapy.

Dr. Lipsky:
Great. And maybe the last question for the day, and I can address this to Dr. Coombs, audience question asks how do you treat CLL after both venetoclax and BTK inhibitors – that double-refractory population?

Dr. Coombs:
That is definitely the most challenging population. Being at an academic center, I definitely explore whether they are eligible for any clinical trials. If they are not eligible for whatever reason I have trouble with that one. I mean, I have used PI3-kinase inhibitors in that setting – typically pretty disappointing response rates and high toxicity burden. I've used chemo, like, once out of desperation for a patient who had a toxicity to a PI3K but, yeah, I mean, clinical trials are definitely the answer, and I think pirtobrutinib will fill that huge area of unmet need when available.

Dr. Lipsky:
Excellent. I absolutely agree with that, and I think it's 12:59, so I'd like to thank everyone for joining us today. I hope you found this information informative and beneficial to your practice. Just as a reminder, you'll receive an email later today with the link to the post-test, and upon completion of the post-test, you'll be able to claim your credits and download your certificate. So, for more information on today's lectures and additional CME activities, you can visit Prova Education and ReachMD, and I'd just like to sign off by thanking my colleagues, Dr. Coombs and Dr. Soumerai, once again, and we hope to see you for future programs. Thank you so much.

Dr. Coombs:
Thank you.

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