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APPlexus Hot Topics 2024: Clinical Updates on Non-Covalent BTK Inhibitors in CLL and MCL

Announcer:
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Dr. Kurtin:
Our first case is an 82-year-old man with relapsed/refractory mantle cell lymphoma, first diagnosed in 2017 stage IVa mantle cell lymphoma, has AFib and obesity as comorbidities. Had his first-line therapy with bendamustine and Rituxan, followed by Rituxan maintenance, and then developed progressive disease. His second-line treatment included acalabrutinib. He had stable disease before a progression with pancytopenia and increasing lymphocytosis. He's about to start pirtobrutinib but is worried about developing infections such as pneumonia.

Dr. Faiman:
So here’s our pre-survey 3, and then I get to turn the reins over to Sandy for a bit. All of the following would be appropriate approaches to manage pneumonia associated with pirtobrutinib except for: 1, administer PJP prophylaxis and herpes virus infection prophylaxis; 2, administer vaccinations according to pneumococcal and live herpes zoster vaccination; 3, before treatment, advise patients to report any signs and symptoms of infection, such as fevers, chills, and weakness; 4, monitor complete blood counts regularly during treatment; or 5, monitor for signs and symptoms of infection, evaluate and treat promptly?

Ooh, this one's tough. Sandy. You made it difficult. I'll give you 3 more seconds, and survey says, B was 76%. So we'll see if that was the correct answer later on.

Pre-survey 4: Which of the following non-covalent BTK inhibitors are being evaluated in combination with venetoclax in ongoing phase 3 trials for relapsed/refractory CLL/SLL? Zanubrutinib and pirtobrutinib; nemtabrutinib and pirtobrutinib; pirtobrutinib and vecabrutinib; or pirtobrutinib alone? Is there a five option there, ‘I don't know’ - I always think we should give that option, unsure, right? Three more seconds, two, one. And we had a 20%, 20%, 30%, and 20% so a broad distribution,

So Sandy, take it away. Provide an overview of BTK inhibitors. Tell us about these covalent, non-covalent, all these above.

Dr. Kurtin:
Thank you very much, Beth. So we are going to focus in this talk on BTK inhibitors specific to the treatment of CLL, SLL and mantle cell lymphoma. And I think the first thing to understand is what is the role of BTK inhibition. So BTK is a part of our B cell receptor pathway, and this is a cartoon to describe that B cell receptor pathway. We all have a B cell receptor pathway. We all have these various mechanisms within that pathway that have to do with the normal development of the lymphocytes. In malignancy, those pathways become aberrant. One of those mutations or those aberrant pathways can be the BTK, or Bruton kinase pathway, which can then lead

to basically the formation of disease. In this case, we're going to talk about CLL, SLL, and mantle cell lymphoma.

The drugs that inhibit BTK mutations work in different ways. So covalent inhibitors bind to something called C481 and block ATP binding, which has to do with cellular development, whereas non-covalent inhibitors reversibly bind to BTK proteins in the ATP pocket, but do not depend on this C481 binding site, and we're going to come back to that a little bit later, a little bit of a delay.

When we look at how well do you inhibit the BTK mutations, we talk about this kinome, this mapping of the protein pathway, and there's a human kinome mapping that maps all proteins. Most of these are small molecules, and BTK resides in this TK domain. So where you see that TK, that's where we want our drug to be working and have the greatest impact. Unfortunately, most drugs have some off-target effect. So you can see that there are little red dots in other domains, which largely describe the side effect profile that we see in these patients. So this is the covalent BTK inhibitors ibrutinib, acalabrutinib, and zanubrutinib. And when we look at the non-covalent BTK inhibitor, specifically the one that is currently FDA approved, pirtobrutinib, this is just a different way of looking at that kinome. You can see that it's very specific to this TK domain where that BTK is located. And then sustained suppression or connectivity selectivity is maintained.

So let's talk about some of the emerging roles of BTK inhibitors in CLL and SLL. These, again, are the currently FDA approved drugs for CLL in the frontline and relapsed/refractory settings. So ibrutinib, acalabrutinib, and zanubrutinib. And I'm going to just touch very briefly on those registration trials that brought these drugs to market. So let's first talk about ibrutinib. This was the first-in-class plus rituximab versus chemotherapy. At the time of this study, we still used a lot of chemoimmunotherapy; that's kind of gone by the wayside as we have these targeted therapies. So the first study is really looking – this is an international trial looking at ibrutinib plus rituximab, compared to bendamustine and Rituxan. You only give six cycles of that, whereas the ibrutinib arms continue on until an unacceptable toxicity or progression of disease. And in the second study, we looked at ibrutinib versus FCR, Ibrutinib and rituximab versus FCR, fludarabine, Cytoxan, and rituximab, again, finite therapy there.

In both cases, there was superiority in the ibrutinib-containing arms, but no significant difference for ibrutinib plus Rituxan versus ibrutinib. So that was a really important paradigm established where we start to see a shift away from rituximab in CLL and SLL toward obinutuzumab. So we'll come back to that a little bit later.

The next studies, here is the ELEVATE treatment-naïve, or TN, not Tennessee, but treatment-naïve, frontline acalabrutinib, so indefinite therapy, plus obinutuzumab, again versus chemoimmunotherapy. In this case, adding in chlorambucil, a drug we used to use all the time in these diseases; don't see it used at all anymore, and largely because of these trials. So in this case, we're evaluating obinutuzumab and chlorambucil, acalabrutinib as a single agent, or acalabrutinib plus obinutuzumab. And again, you can see that the progression-free survival was significantly higher for the acalabrutinib-containing arms versus obinutuzumab and chlorambucil. And you can see that the acalabrutinib plus obinutuzumab also fared very well here. A little delay in my slide transition. Sorry about that.

The next drug that's currently FDA approved to zanubrutinib. And again, this is a trial, the SEQUOIA trial, looking at indefinite zanubrutinib versus BR, again, bendamustine and Rituxan. And there's different cohorts here, where we're looking at del(5q) or the lack of del – or excuse me – 17p, and that's a critically important factor in these diseases, because it carries a very poor prognosis if you are positive for 17p which essentially is equivalent to TP53 mutations. So in this case, again, we're looking at zanubrutinib, indefinite therapy compared to BR. And again, you can see the superiority here in progression-free survival.

So with all that in mind, this is now the way we look at newly diagnosed patients with CLL and SLL. And we're going to first of all establish TP53 status or deletion 17p. We know that in that instance, chemotherapy has no role with one exception, and that is the immunoglobulin variable heavy gene mutated in younger patients who have no comorbidities where FCR still can play a role – excuse me, this is without 17p. And then if we look to the left of that, there's a whole menu of options for possible treatment in these patients. We're going to again focus on BTK inhibitors in this discussion. And then to the right of that is the patients with 17p, where you see really no chemotherapeutic options.

So what is the best therapy? There is no single best initial therapy to date, so there's a lot of variability in what people might select as frontline therapy. Some of the data across these trials is out further than others. You can see there's a 5-year follow-up, 6-year follow-up, some of these studies are going toward 7-year follow-up data, so durable data. Some are newer because they are newer to the market, but right now there is no established frontline therapy. There we go.

So let's talk about relapsed/refractory now. So this is a important study. They ELEVATE-RR trial, looking at noninferiority established by central review, independent review, and again, looking at progression-free survival, and comparing acalabrutinib and ibrutinib. This was a very important study, all of the early BTK inhibitor studies compared to ibrutinib, which was first in class. And so this is basically establishing that the outcome for progression-free survival was similar across those two regimens. What was important in this study was a difference in tolerability. And this provided another shift in the current NCCN guidelines in terms of preferred regimens, because the

adverse event profile of acalabrutinib was better than that for ibrutinib across multiple toxicities. And because of this, ibrutinib no longer carries the preferred as a therapy in this setting, it is still considered as an option.

Then the ALPINE study, another really important study, doing a very similar comparison here, where now we're talking about zanubrutinib compared to ibrutinib again until – this is indefinite therapy, until progression or unacceptable toxicity. And this did stratify patients by TP53 mutation status. So also important to consider that as an included marker here. And this showed, again, superior outcomes in the zanubrutinib arm relative to progression-free survival, and this was regardless of TP53 status. So also very important to understand. It also looked at those toxicities that we might associate with BTK inhibitors, and I'll come back to that a little bit later. And zanubrutinib was associated with lower rates of AFib, flutter, cardiac events, leading to treatment discontinuation, very similar to what we saw in the data comparing acalabrutinib to ibrutinib.

So acquired resistance to covalent BTK inhibitors is generally driven by this mutation at the C481 site, as I mentioned. And that really differentiates the covalent BTK inhibitors from the non-covalent BTK inhibitors, which we're going to talk about briefly. That's nemtabrutinib and pirtobrutinib, which do not rely on that C481 binding site. And so this offers an opportunity for using a BTK inhibitor, a very important therapeutic option in these patients, in the setting of resistance based on the covalent BTK inhibitors.

So the first thing to talk about here is the BRUIN trial. This is updated results now with the non-covalent BTK inhibitor, pirtobrutinib. Again, phase 1/2 study, dose escalation expansion in phase 1 and looking at different dosing regimens, as is very common in that trial design. Primary endpoint, maximum tolerated dose, and then again, making a recommendation for what the final dose was. And based on this trial, very recently, December 1st of 2023, this granted accelerated approval to pirtobrutinib for adults with CLL/SLL who have received greater than or equal to two prior lines of therapy, including a BTK inhibitor and a BCL2 inhibitor. So that was the approved indication. And as with all accelerated approvals, they can be subject to data further down the road in later-phase clinical trials.

And so you say, okay, response. What does that look like? And you can see here the overall response rates for either prior BTK inhibitor or prior BTK plus a BCL2 inhibitor were 83 and 79.7%, so very important across those two groups who had prior exposure to BTK inhibitors, with or without a BCL2 inhibitor.

And then you say, okay, what about safety? And so if we look at those key areas, that special interest area where we're really particularly concerned about infections in CLL and SLL, particularly sinopulmonary infections, you can see that that all causes were roughly 30, almost 31%, but grade 3/4 was about 4.3%. And then we look at hypertension, AFib, flutter, the bleeding problems, very low numbers in grade 3 or greater toxicity. So comparing to other BTK inhibitors, looking to be either similar or better than some of those agents.

So how does this look then when we try to sequence patients? Again, you know, a lot of it is dependent upon their TP53 or 17p status, their immunoglobulin variable heavy gene doesn't necessarily select therapy unless it's mutated, and they don't have 17p, where we might consider FCR. But otherwise, we're going to really talk about a BTK inhibitor or BCL2 inhibitor plus or minus a monoclonal antibody. And then, depending on whether they have finite therapy or we have indefinite therapy, we are going to probably either switch to a different class, unless we stop because of adverse events. So if they're responding to a BTK inhibitor and you stop because of adverse events, you would possibly select another BTK inhibitor. And if you are stopping because they've developed resistance, you would go from a covalent to a non-covalent BTK inhibitor. So all of this sequencing is really still being worked out, as there are more options and these data mature.

And then lastly, the BELLWAVE-001, trial. This is now that nemtabrutinib. And this is again, relapsed/refractory CLL and SLL, again, single-arm dose-expansion, phase 1/2 study. So very similar design. And so this is an emerging, bioavailable, reversible, non-covalent inhibitor of BTK and C481S mutant BTK. So again, non-covalent, not requiring that C481S binding for efficacy. And early data is looking very promising. The most common grade 3 or greater AEs are neutropenia, febrile neutropenia, and pneumonia, not uncommon across this class of drug.

So Beth, I'll hand it back over to you.

Dr. Faiman:
Thank you. So for our assessment 2: According to current guideline recommendations, which of the following patients would be a candidate for an approved non-covalent BTK inhibitor: previously treated CLL following two previous lines of therapy, including a covalent BTK and BCL2 inhibitor; previously treated mantle cell with one prior line of therapy, including a covalent BTK inhibitor; previously treated CLL following three or more prior lines of therapy; or previously treated mantle cell following 4, this is the BRUIN trial, if you can remember.

We'll give you about 5 seconds for this poll, and then Sandy is going to share the rationale after I tell you how you all did. There's so

much to learn, and that's why these programs by PCE and CCO and others are so important. 3-2-1, survey says – okay, so we started out with a 43% selected B, and currently we have A for 38%, B for 30, C for 28, and D is 2%. So a little bit different spread. Did we get an increase gain in knowledge from 21% to 38%? So we did. Yay! Correct answer.

Sandy, share with us your rationale.

Dr. Kurtin:
And I know this is a lot of information to take in, and particularly if you aren't you know, involved in managing patients, you know, with CLL and SLL, but the correct answer is 1, based on that BRUIN trial which I just mentioned. So looking at CLL following two previous lines of therapy, including a covalent BTK inhibitor and a BCL2 inhibitor. And if you recall from the BRUIN trial, patients receiving a pirtobrutinib responded, regardless of prior BTK inhibitors, the covalent BTK inhibitors. And so that would be our next choice for this particular patient. It has also received approval for patients with relapsed/refractory mantle cell lymphoma after greater than or equal to two lines of systemic therapy. We're going to talk about that next, including a BTK inhibitor.

All right, so let's go right into mantle cell lymphoma. So mantle cell lymphoma, a subtype of non-Hodgkin lymphoma, can be very difficult to treat. Historically, was included in the indolent lymphomas. And then really we came to realize that it's not in most cases; we have a subset of patients who really behave in an indolent way. But in those patients with bulky disease or stage III/IV disease, this becomes much more challenging. And so one of the very first questions is we look at eligibility for a stem cell transplant, an autologous stem cell transplant, because of the probability of relapse in those patients with more advanced or aggressive or poor-prognosis disease. And so this study is looking at – or this paradigm is looking at, are they a candidate or not a candidate for stem cell transplant? And then what are those preferred regimens? And some of these we've been using for a very long time. Others are a little bit newer. But the aggressive regimens can be very challenging for patients to endure. And, you know, so this is why we say, are they eligible for more aggressive therapy?

If they're ineligible, then we look at other options that include various chemotherapy combinations, plus or minus monoclonal antibodies, and also looking at the role of BTK inhibitors. In this case, looking at acalabrutinib and plus rituximab in these current guidelines.

One of the options in that transplant-eligible arm is the TRIANGLE study. It's the regimens that were studied in the TRIANGLE trial. And this is a randomized, open-label, three-arm, phase 3 trial. So very well-designed study, again, looking at stage III/IV mantle cell lymphoma, less than age 65, suitable for more aggressive therapy, including a stem cell transplant. So stem cell transplant is really looking at consolidating that response, and this is answering that question, does transplant basically still play a role in these patients? Yes or no? And does maintenance therapy play a role post-transplant? So if you look at the green arm, those patients get their initial therapy, they get transplant, they go on to receive maintenance, and then on to observation. And basically, ibrutinib, which was in one of those arms, did not increase the chemotherapy combination; it did increase serious infections, however, after stem cell transplant. So arm A plus ibrutinib was more toxic versus arm A or arm I alone, and so that was a consideration in updating those NCCN guidelines.

The other thing that this basically solidified was chemotherapy, stem cell transplant versus chemotherapy plus ibrutinib failed to show superiority for survival. Only approximately 54 to 58% of patients received rituximab maintenance. And after a median follow-up of 31 months, there was no overall survival benefit with adding stem cell transplant to ibrutinib. The data are still immature for statistical significance. So the bottom line is the covalent BTK inhibitor category 2A for ibrutinib, category 2B for acalabrutinib or zanubrutinib as an option in the frontline, intensive induction therapy for these patients with stage III/IV mantle cell lymphoma. And so this is how those guidelines look now and again. These are constantly evolving as we have new therapies. So you can see the frontline - the second line therapies here for covalent BTK inhibitors, acalabrutinib, zanubrutinib, this is now second line. You can have R squared or lenalidomide plus rituximab, and then other recommendations, ibrutinib is listed there based on that study. And then we have the non-covalent BTK inhibitors in the third-line setting, the pirtobrutinib, we also find now CAR T in that setting. And then there are other things that can be considered in the second line.

So you can see this voluntary withdrawal in the U.S. for ibrutinib based on that study that we just discussed. And so now we see acalabrutinib and zanubrutinib as our covalent BTK inhibitors, and you can see the difference in overall response rates there, acalabrutinib and zanubrutinib, 99 and 72%, 12-month progression-free survival 67 versus 75.5 in those two different regimens, and then median overall survival in months is not reached. So these are evolving data at 12 months, 87 for the acalabrutinib, 84 for zanubrutinib, and not reported at 18 months. So again, the data is maturing here. The median follow-up of basically 16 months, which is why we don't know those answers yet.

So now, when we look at covalent BTK inhibitors in now relapsed/refractory mantle cell lymphoma, basically it's important to ensure that the therapy is personalized by accounting for individual patient characteristics and clinical scenarios. So where did they start? And where are you moving to? So ibrutinib no longer indicated for relapsed/refractory mantle cell lymphoma in the U.S. because of what

we've discussed. It does have better CNS penetration, so we do think about that if people have CNS disease, obviously that's a very bad prognosis. Acalabrutinib, no head-to-head comparison with zanubrutinib and vice versa. So that's some limitation in looking at the tables that we looked at previously. Those are not head-to-head comparisons; those are just simply data reported from those trials. Acalabrutinib is FDA approved for relapsed/refractory mantle cell lymphoma, has higher incidence of headaches. Zanubrutinib also FDA approved for relapsed/refractory mantle cell lymphoma, has higher rates of neutropenia. So really we're going to look at if they progress on a covalent BTK inhibitor, outcomes are poorer. Subsequent strategies, we really want to try to get them involved in clinical trials.

We do know, however, that in mantle cell lymphoma, the C481 site does not play a role. There are different underlying mechanisms for BTK inhibitor resistance. These are evolving in the data, and we're trying to better understand what that difference is in the mantle cell lymphoma versus CLL and SLL mechanisms.

So the BRUNE trial for pirtobrutinib also included previously treated mantle cell lymphoma. So dose escalation and dose expansion. In this case, we have mantle cell lymphoma, again, greater than two - or equal to or greater than two prior lines of therapy, had to have an adequate performance status, and again, a dose finding, and then looking at secondary endpoints for pharmacokinetics, overall response, rate, duration of response, progression-free survival, and overall survival. So here is the response. And these are patients who had received prior BTK inhibitors, versus those who are BTK inhibitor naïve. And you can see the difference in the outcomes, the patients who were covalent BTK inhibitor naive, had overall a better response than patients who were previously treated with a BTK inhibitor, so a covalent BTK inhibitor. But nonetheless, there was a response, although we know generally those patients don't do well overall. So this is important data to show that there still can be a response in the same class of drug with a slightly different mechanism of action. So an important paradigm was established here.

And then, of course, looking at safety profiles. Again, if we look particularly at those special areas of interest, again, infections, definitely something again to consider in any B cell malignancy. But this is something in BTK inhibitor, or the small molecules in general, we are particularly concerned about in these patients. But when we look at grade 3 or greater, not a significant number of patients there. And then we look at the other areas of bleeding and bruising and hypertension, AFib, flutter, where grade 3 or greater were really very minimal, if none. So very important to look at that toxicity profile in patients who may have had a prior BTK inhibitor, as we're talking to those patients about what they might experience and what they might have concerns about.

Dr. Faiman:
So here we go. Yeah, for our interactive session -

Dr. Kurtin:
On January 27th, so very, very recent approval. So that's exciting to add that to our arsenal.

And I will send it back to you, Beth.

Dr. Faiman:
Thank you, Dr. Sandy, we're going to have a little bit of an interactive discussion now in the middle of this program with a real-world patient case. This is a 68-year-old woman with CLL harboring deletion 17p which, if you don't have a tumor suppressor gene in any cancer, that's not necessarily a good thing. A 68-year-old was diagnosed as 90,000 white cells, hemoglobin of 8.5, platelets of 60,000. Her medical history was clinical depression. She was receiving a serotonin antagonist. She had controlled headaches with medication, AFib, direct oral anticoagulant, rivaroxaban, apixaban, one of those bans. She received acalabrutinib and had achieved MRD after 1 year of therapy, which is sustained; however, she developed increased frequency and intensity of headaches that aggravated her depression, persistent nausea, interfered with appetite, and progressive fatigue. That sounds horrible.

I'm going to ask you, audience members, to answer this poll, and then I would like to hear what Sandy would do for this patient. Considering the available information, which the following is the next best line of therapy: keep her on acalabrutinib and do a better job managing her symptoms; bendamustine/Rituxan; ibrutinib; pirtobrutinib; or zanubrutinib? Take about 5 more seconds. 4-3-2-1. And the survey says, 3% of you said, keep her on acalabrutinib and do a better job. Thankfully, that was all. Pirtobrutinib was 48%, bendamustine 22, ibrutinib 14, and zanubrutinib 11.

Sandy, what would you do for this patient?

Dr. Kurtin:
Well, we would, you know – she's responding, she's maintained undetectable MRD. So switching to a different BTK inhibitor would be appropriate. And in this case, you know, given the lines of therapy, we would consider switching her to one of the other BTK inhibitors that has a different toxicity profile. In this case, probably zanubrutinib.

Dr. Faiman:

Yeah, absolutely. And I would do the same thing. You know, she has atrial fibrillation, so ibrutinib makes it a less favorable target. And pirtobrutinib, as you mentioned, with the lines of therapy, she has only had the one prior line of therapy. So zanubrutinib, it is. That's what I would do. And it sounds like you as well. But you know, again, take into account patient characteristics, their comorbidities, etc., is all important.

What about the next patient case? This is an 80-year-old man with a CLL without deletion 17p. He's diagnosed with bulky retroperitoneal and mesenteric adenopathy. White count is 80,000 hemoglobin, 10.2, platelets 120. His medical history includes diabetes treated with insulin and oral antidiabetic agents, gastroparesis, and GERD, and he has a proton pump inhibitor and chronic kidney disease. So pretty common patient, right? He receives zanubrutinib as first-line therapy, and achieved that uMRD for 1 year and then disease progression, and then receives venetoclax/obinutuzumab as his second-line therapy. He develops grade 4 hypersensitivity to obinutuzumab after two doses. And with the venetoclax ramp-up, he developed grade 3 diarrhea and dehydration, which did not agree with his chronic kidney disease. Patient declined continued therapy with ven/obinutuzumab. His mutational analysis to BTK inhibitor resistance the C481 mutation positive, acquired TP53 mutation, and del-17p.

So considering the available information, which of the following is the best next line of therapy: acalabrutinib; ibrutinib/venetoclax; idelalisib/rituximab; lenalidomide/rituximab; or pirtobrutinib? 80-year-old guy. I'm always interested to see how people answer these polls. Let's close it out in 3 seconds, 2-1, and the survey says 8% acala, 5% ibrutinib, 41% pirtobrutinib, 26% RR or R2. Sandy, what would you think?

Dr. Kurtin:
Well, he meets criteria for pirtobrutinib. Again, you know, he's had a prior BTK inhibitor. He has that resistance profile. But pirtobrutinib, as a non-covalent BTK inhibitor, is not reliant on that mutation. And idelalisib and rituximab is not a preferred regimen. Lenalidomide and Rituxan also probably less likely to help in the setting of 17p and TP53. We've already talked about the issues with ibrutinib and toxicity profiles. So pirtobrutinib would be the choice.

Dr. Faiman:
Yes, I agree 100%. You know, acala is not really recommended in the BTK C481 mutation, and most of you knew the correct answer anyhow. So good job, Sandy, for your learnings, today. I'm going to send it back over to you for the rest of the presentation.

Dr. Kurtin:
Thank you, Beth. Sorry about the delay of the slide. There we go.

So let's talk a little bit more about adverse events and what we might do about them. You know, there are what we consider class effects for BTK inhibitors, like many drug classes that we use. And across the board, if you're treating a hematologic malignancy, you are going to expect some level of cytopenia. And so this is not, you know, shouldn't be a surprise to us, I guess. There is a little bit more neutropenia, as I mentioned previously with zanubrutinib, but otherwise, across the board, cytopenias are expected. I think infections, particularly sinopulmonary infections, are things that we worry about in B cell malignancies in general and so across these covalent BTK inhibitors, there are similar data here, zanubrutinib having slightly increased grade 3 or greater infection rates. And then among those class effects that are a little bit more unique to BTK inhibitors and certainly in the early days of BTK inhibition, this became a big issue. And some of the trials, and I didn't really call that out because of all the time, but some of those trials were designed intentionally, where patients could not be on blood thinners. And we all have to become much more comfortable with how to manage either direct oral anticoagulants or warfarin, Coumadin in those patients who require it with very careful monitoring. But nonetheless, bleeding and hemorrhage and bruising can be pretty significant in some of these patients. This was largely one of those factors that had ibrutinib sort of fall off in being a preferred regimen, certainly in the frontline setting. And so just being aware of this is important, and monitoring it closely.

And there are a subset of patients where it may not be recommended. If you do have patients where you might see more severe thrombocytopenia, that's a particular area that needs to be focused on and managed in terms of regulating that anticoagulation. Lymphocytosis, not a surprise; this is just basically moving those lymphocytes out of the nodal regions into the peripheral blood. And so we will see this across drugs, particularly in the initiation of therapy. And then looking at the GI effects, these are oral compounds, not a surprise that you can see some GI toxicity, again, more severe with ibrutinib here.

But honestly, when we start talking about the our patient, who we stop, not because of lack of response, but because of tolerance, some of how we choose drugs when we have more than one choice, and why there isn't a preferred trial in many cases, is based on this toxicity profile. So familiarizing yourself with that and looking at the patient in front of you and deciding what might be the best fit for that patient so they can continue on therapy as long as indicated and as long as they are benefiting.

We do see some arthralgias and myalgias across these drugs. Very similar incidents here. And then there are those others. So

headache is something that is reported, particularly with acalabrutinib, also seen with ibrutinib, much less prominent in zanubrutinib. Can see rash across all of these, although generally, we're able to treat through that. And then fatigue is fairly universal across all these patients, regardless of regimen.

So what are we going to do about that? For AFib, you know, you can't see AFib, but you have to hear AFib. And even with that, you need to do EKGs. You're going to really think about, is it rate controlled? Are they on a direct oral anticoagulant? Do they have a cardiologist? If not, you might want to get one so you can help comanage.

And then bleeding events, the important thing here, really again, is, if they are on a anticoagulant, and they need to be on that anticoagulant. Patients with mechanical valves, particularly, it's very hard to negotiate with the cardiologist to discontinue. And then there's really the necessity to account for surgeries. And so if they're just going to have, you know, a root canal, you know, that's not fun, but that's probably not a big risk to them. They're having an extraction, that's a different level of risk. So understanding the degree of the severity of the surgery, the risk of bleeding with that surgery. If it's an open abdominal surgery, you're going to really need a whole week ahead of surgery off of the BTK inhibitor. So gauging the amount of time you need to hold the drug before or after surgery is going to depend on the surgery itself and then other factors for that patient, in terms of risk of bleeding, bleeding history, etc.

Diarrhea, again, we know how to manage this. Headaches, we can try to do better with managing headache. There are a variety of drugs that can be tried. You know, caffeine-containing compounds, other drugs, narcotics don't generally work well. So the opioids aren't generally very effective here. This mechanism isn't completely well understood relative to acalabrutinib in particular. But these can be fairly severe in our patient. Where they already have a history of problems and it exacerbated depression, that's where we would say, you know what, we're going to see if we can have a BTK inhibitor, you know, that's effective without the same level of headache. In that case, zanu.

So this is just an algorithm that might – oh, I'm sorry. Hypertension, again, this can happen much later on. So this doesn't happen necessarily early, but they can go on much later. Infections, we are going to prophylax patients for opportunistic infection. We are not going to give live virus vaccines ever in these patients, so they have to be attenuated, and so we would never use the live herpes virus vaccine, they can have the attenuated vaccine. We do want to particularly pay attention to PJP prophylaxis for these patients, because of the suppression of those B lymphocytes directly. And then really be aggressive in early identification and mitigation of their infection. In my patients, I say don't go to urgent care. I want you to call us first, because we're going to react differently to their infection when we know that they have a B cell malignancy and then are on these drugs. And then musculoskeletal pain, you know, we can use our typical interventions. We use dose modification and supportive care to treat cytopenias. So those are the covalents.

And then when we look at how we switch, again, intolerance, you know, they're responding, but they're intolerant, you are going to look at, you know, what you did, what's recommended next, and then whether or not those side effects might recur. So, this is an important slide to say if in 33 patients can tolerate ibrutinib, having 61 AEs, switch to acalabrutinib, 13% recurred at a lower grade, 72% had no recurrence of AEs, 41% on ibrutinib switched to acalabrutinib across 43 AEs, with CLL, again 44% recurring at a lower grade, 41 no recurrence of AEs. And then ibrutinib to zanubrutinib, or acalabrutinib to zanubrutinib, 23% and 6% with acalabrutinib recurred at a lower grade, 70 to 83% had no recurrence of AEs that were associated with ibrutinib or acalabrutinib. So in our patient, this is where we would say they're responding, unacceptable toxicity, we're going to switch to zanubrutinib.

When we look at pirtobrutinib, AEs of interest, you know, the AEs very similar across the BTK inhibitors in general, but again, monitor for those signs and symptoms of infection, early intervention, prophylaxis. And again, you want to use PJP prophylaxis, the appropriate vaccines, no live virus vaccines. And in some cases, depending on the region of the country, we have valley fever here in Arizona, which is a spore and the fungal family, so we put them on prophylaxis for that. And in some cases, if they've had recurring infections, there may be an appropriate role for other antimicrobial prophylaxis.

The hemorrhage, very much the same management. Cytopenia is the same management. The cardiac AEs, if you remember the data, those numbers were for grade 3 or greater were much smaller, but not zero in some cases. So again, getting them set up with a cardiologist, making sure that you're monitoring their symptoms, getting EKGs when you're needing to.

Secondary primary malignancies, so we didn't really talk about, but this is something that is true across all B cell-directed therapies, regardless of drug, and this is true for the BTK inhibitors, whether covalent or non-covalent. So all of my patients with B cell malignancies, I get them established with dermatology. We live in sunny Arizona, where we got a lot of sun exposure across the years, and so we get them set up for skin checks on a regular basis.

And the motto is, if in doubt, cut it out.

And Beth, I'll hand it back to you.

Dr. Faiman:
Sure. So 82-year-old man with relapsed/refractory mantle cell, diagnosed in 2017 with stage IVa. Comorbidities, AFib and obesity. Frontline therapy BR, followed by R maintenance. Second-line acalabrutinib. Stable disease before PD, with pancytopenia and lymphocytosis. He's about to start pirtobrutinib, and is worried about infections such as pneumonia.

So assessment number 3, all of the following would be appropriate approaches to managed pneumonia, except which one: administer PJP and herpes virus prophylaxis; administer vaccinations, including pneumococcal and live herpes zoster vaccination before treatment; advise patients to report any signs or symptoms of infection; complete blood counts regularly, monitor during treatment; or 5, monitor for signs and symptoms of infection, evaluate and treat promptly? Remember what Sandy just said? She gave you the answer on a silver platter. So let's see in three more seconds, if this is correct, 3-2-1, and the survey says, yay, 87% said, don't give a live herpes zoster vaccine. Sandy, do tell us. Do you agree?

Dr. Kurtin:
Yes, just as I said, we would never give live vaccines to anybody with a B cell malignancy. And really, now, when we have attenuated vaccines, we pretty much don't use them in anybody that's immunocompromised, regardless of solid tumor, liquid tumor, because why take that chance? So you would not give live herpes zoster vaccines?

Dr. Faiman:
Perfect. All right.

Dr. Kurtin:
Okay, so we're going to wrap up with just some of the emerging data. There's so many things happening. It's a great time in the science across diseases, but this is really looking at BTK inhibitors in CLL, SLL, and mantle cell lymphoma. And so a couple of the exciting data is the CAPTIVATE trial. In this case, they are looking at ibrutinib plus venetoclax for untreated, so previously untreated or treatment-naïve CLL and SLL. This is a multicenter, randomized, phase 2 study looking at ibrutinib for three cycles – sorry, age less than 70, active disease, adequate performance status. So ibrutinib for three cycles at 420 mg, then adding to that, venetoclax ramp-up. And so the idea here is that you sort of debulk with the ibrutinib. You do the venetoclax ramp-up, similar to debulking with a obinutuzumab, where then you reduce the risk of tumor lysis as you introduce the venetoclax. So then you have ibrutinib plus venetoclax. And then if they're undetectable MRD, there's a double-blind looking at ibrutinib versus placebo as maintenance, or if they have detectable disease, ibrutinib versus ibrutinib plus venetoclax and 1-year disease-free survival confirmed by undetectable MRD inpatients randomized to the MRD cohort, and then CR rates for the fixed duration cohort, were the primary outcomes or endpoints. Secondary endpoints, detectable MRD rates, progression-free survival, overall survival, and safety.

Okay, thank you.

And so you see here that the primary endpoint, 56% achieved a CR, 24-month progression-free survival rates, very, very good in peripheral blood and still in bone marrow, 92% of the patients finished that study.

And then the second one is the CLL2-GIVe, obinutuzumab plus ibrutinib plus venetoclax for untreated CLL with deletion 17p, TP53. And you can see here, there's the combination of those three drugs, and they do a final restaging at cycle 15, stop the ibrutinib if they have undetectable MRD, or go on to ibrutinib continuation if it's positive there. And these outcomes are really very exciting. You can see the CR and PR rates here. Collectively, the overall response of 100%, hard to beat that. And the depth of response measured by MRD, initially very good. It is waning off a bit. And so that's important to consider.

So some of the other trials that are going on, phase 3 trials, that include the non-covalent BTK inhibitors. You can see there are a number of trials here with pirtobrutinib, looking at different groups of patients, and then also nemtabrutinib, also across multiple groups. And then in mantle cell lymphoma, a number of trials using both of those agents, as well as some of the covalent BTK inhibitors acalabrutinib and zanubrutinib.

Dr. Faiman:
Great. So we're going to revisit our survey. This is the last one. Which of the following non-covalent BTK inhibitors are being evaluated in combination with venetoclax in ongoing phase 3 trials for patients with relapsed/refractory CLL or SLL: zanubrutinib and pirtobrutinib; nemtabrutinib and pirtobrutinib; pirtobrutinib and vecabrutinib; and pirtobrutinib alone?

Why can't I say that word? It's been a day of not being able to pronounce words, I'll tell you. You missed the first few, Sandy, with the bladder cancer. Forget it.

I'll give you 3 more seconds, 3-2-1, and survey says, the pretest was – oh, no that's a post-survey. Pretest was 32% for option number B, letter B, and then 48% for the second one. And the correct answer, Sandy?

Dr. Kurtin:
Is B, nemtabrutinib and pirtobrutinib. So looking at them in a variety of combinations. And so, yes.

Dr. Faiman:
Perfect. Great. So here we are on the overall conclusions. This is back to you.

Dr. Kurtin:

Sorry, there's a delay in the two slides. Moving. Here we go. Sorry.

So really limitations of monotherapy versus the benefits of combination therapy, I think we're learning about how to combine these with other small molecules across classes plus or minus anti-CD20 monoclonal antibodies. There are some limitations to BTK inhibitors, you know, low complete remission rates, depending on, you know, the trial that you look at. The indefinite therapy, that that becomes a financial burden on the patient. Some of, you know, treatment fatigue, adverse event profiles needing to be very much individualized, and then that development of resistance, which we've spoken to, where you might consider switching classes or switching to a non-covalent BTK inhibitor. Certainly, benefits of fixed duration therapy in some of these trials. Deeper response rates, we saw some exciting data there. Less resistance and synergy of mechanisms when doing these combinations. And then the ability to have all oral therapy is pretty exciting for those patients, in terms of just the time commitment and logistics involved. Certainly, things that have to be considered are comorbidities, disease factors, that disease burden, their mutational status, the toxicity profile, and then looking at adherence across all of these agents that are oral.

Dr. Faiman:
So for our assessment 1, How confident are you in your ability to describe to patients the differences between covalent and non-covalent, their molecular characteristics, etc.? You can read all of the key points that we've discussed today. Rate 1 to 5, not confident, slightly confident, neutral, somewhat, or very confident. A lot of new material we've discussed today in this last 6 hours together. And we'll give you 3 more seconds, 2-1, and ooh, people are more confident now. Thank you for being more confident after Dr. Kurtin's talk. This has been wonderful. We're going to go to our audience question and answer after I ask you, Do you plan to make any changes in your clinical practice? The answer is yes, no, or uncertain. Two, and I always hope you choose yes, whether you really are able to at least you've come by confidently hoping that you can.

Poll number 6, please take a moment to text in one key change that you plan to make in your clinical practice based on this education.

We do have just a few minutes left for question and answer. I can't believe we're at the end today. We had a question, How is B cell malignancy symptoms presentation different from T cell?

Dr. Kurtin:
You know, that can be difficult. T cells are lymphocytes also, but I think that, you know, certainly in the non Hodgkin's lymphoma bucket, including CLL, SLL, and mantle cell lymphoma, you know, B cells act differently than T cells in terms of their immune processes. Patients with T cell malignancies may or may not have bulky adenopathy and they don't have the same high white blood cell counts that play into those things like fatigue, night sweats, bone pain, sometimes all of those, right?

Dr. Faiman:
Very difficult.

Dr. Kurtin:
So it's just different.

Dr. Faiman:
Absolutely. And then do BTK inhibitors increase all-cause mortality?

Dr. Kurtin:
I don't think you can say that. I think that there, you know, that we looked at the grade 3 or greater, in some trials grade 5, I think that in general, they can be very well tolerated. And then those patients who do experience toxicity, we have really become much more comfortable in managing them.

Dr. Faiman:
Yeah, absolutely. I agree 100%. Advanced practitioners are well suited to identify the headaches and dose reduce and holds and make sure you hold before surgery. You know, bleeding risk, things like that. So I think you play a pivotal role into keeping your patients alive while on BTK inhibitors. And then finally, how does the live vaccine work with B cell malignancies. Why shouldn't we do a live vaccine?

Dr. Kurtin:

Well, live vaccines are live, so you're basically injecting a live virus, which is like giving you shingles to stimulate your immune response to make antibodies. So you basically can give people very serious cases of shingles, which can be lethal. So you would never give a live virus of any kind to a patient with a B cell malignancy.

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