## Transcript Details

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# Noncovalent BTK Inhibitors: New Targeted Options for Relapsed or Refractory Chronic Lymphocytic Leukemia and Mantle Cell Lymphoma

**Announcer:**
Welcome to CME on ReachMD. This activity titled, " Noncovalent BTKInhibitors: New Targeted Options for Relapsed or Refractory Chronic Lymphocytic Leukemia and Mantle Cell Lymphoma" is jointly provided by Medical Education Resources and Plexus Communications and held in partnership with the CLL Society.

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**Dr. Davids:**
Hello. I'm Dr Matthew Davids from Dana Farber Cancer Institute where I serve as the Director of Clinical Research in the Division of Lymphoma. I'm also an Associate Professor of Medicine at Harvard Medical School here in Boston. Today's program is titled “Noncovalent BTK Inhibitors: New Targeted Options for Relapsed or Refractory Chronic Lymphocytic Leukemia and Mantle Cell Lymphoma.”

These are our learning objectives.

And here's an overview of what we'll discuss today. We'll start by talking about a general overview of noncovalent BTK inhibitors, then we'll move on to talk about BTK inhibitors in mantle cell and CLL, we'll focus on the safety profile of noncovalent BTK inhibitors, and then we'll talk about specific patient selection and treatment sequencing for MCL and CLL.

Just to remind you, there's a number of currently FDA approved targeted therapies for CLL and mantle cell lymphoma. For the BTK inhibitors, there's now three covalent inhibitors that are approved, ibrutinib, acalabrutinib, and zanubrutinib. We also now have one noncovalent BTK inhibitor FDA approved, that's pirtobrutinib, just approved in 2023. There's an investigational noncovalent BTK inhibitor, nemtabrutinib, that's now in late phase clinical trials as well. And I'll highlight venetoclax, the BCL2 inhibitor first approved for relapsed/refractory CLL in 2016 and later approved as a frontline therapy for CLL in 2019. These BTK inhibitors differ in terms of their specificity, mechanisms of action, and potential for off-target effects.

Here you can see KINOMEscan plots, which give you a sense for the specificity of each of these five different BTK inhibitors. The top three are the covalent inhibitors. And as you can see, ibrutinib has many different targets, including BTK, whereas acalabrutinib and zanubrutinib still effectively target BTK, but don't tend to have as many of these off-target effects on different kinases. At the bottom, you see the two noncovalent, also known as the reversible inhibitors, pirtobrutinib and nemtabrutinib. Pirtobrutinib is probably the most selective of all these BTK inhibitors for BTK, nemtabrutinib does have some off-target effects, but is also relatively selective for BTK.

As we'll see in some detail during the presentation, acquired resistance to the covalent BTK inhibitors in CLL is generally driven by mutations at BTK of C481 or related residues. Here you can see the BTK gene and all the different domains. And you see on the right that the kinase domain, which is where these drugs bind, is typically the site where their resistance mutations can arise. And these

mutations can develop in patients on any of these different covalent BTK inhibitors. And it's best characterized in CLL. The presence of these mutations is less well known in mantle cell lymphoma. So again, pirtobrutinib is a highly selective BTK inhibitor. You can see this on the left. In the middle, you can see that the plasma exposure exceeds the IC90 for targeting BTK throughout a 24-hour dosing interval, and this allows pirtobrutinib to be given as a daily drug. On the right, you can see some of the theoretical ideas around how pirtobrutinib may stabilize or maintain BTK in a closed, inactive confirmation which allows it to continue to inhibit the enzyme even in the presence of resistance mutations. So in contrast to the covalent BTK inhibitors, we think this is why pirtobrutinib is able to be effective even in the presence of these disruptive resistance mutations. This gives you another sense of how noncovalent BTK inhibitors like pirtobrutinib do overcome resistance. So on the left, you can see where the covalent BTK inhibitors, ibrutinib, acalabrutinib, and zanubrutinib bind. You can see that they require the C481 residue in order to establish a covalent bond with the enzyme. On the right, you can see that pirtobrutinib, as a noncovalent inhibitor, can target in a slightly different way, such that it does not require the C481 residue in order to bind to the kinase domain. So whether the C481 is wild type or mutated, pirtobrutinib can still be equally effective.

So with that by way of general introduction, now let's dive a little bit deeper into mantle cell lymphoma and the role of noncovalent BTK inhibitors in this disease. Remember that most patients with mantle cell lymphoma are still getting chemotherapy-based regimens in the frontline setting. Here you can see the variety of different options for relapsed/refractory mantle cell lymphoma. Most patients these days are getting covalent BTK inhibitors in this second-line setting, and acalabrutinib and zanubrutinib are the ones most commonly being used. As we get into later lines of therapy, we also have access now to a CD19-directed autologous CAR T-cell product brexu-cel. We have the approval of the noncovalent BTK inhibitor, pirtobrutinib, and then other options that are listed in NCCN guidelines, like bortezomib, lenalidomide, with or without rituximab, or using chemotherapy again.

Other therapies that are either in development or working toward approvals include liso-cel, glofitamab, which is a bispecific CD20/CD3 antibody, venetoclax, the BCL2 inhibitor, and treatments that target ROR1, which is an antigen pretty specific to B cell malignancies.

So unfortunately, when patients with mantle cell lymphoma relapse, the disease is usually quite aggressive, and most patients will ultimately experience disease progression. Historically, outcomes for this group are poor, with a median overall survival of less than 1 year, and the mechanisms of resistance to therapies are less well understood compared to CLL. Fortunately, the covalent BTK inhibitors have made a big impact here, with many patients getting 2 to 3 years of progression-free survival in that setting. However, what I'm showing you here are data of what happens post covalent BTK inhibitor-based therapy. For all patients, the median overall survival was only 4 months in that clinical scenario. And for some patients who could not make it onto additional lines of therapy, the survival was median of less than a month. So options for these patients now include the noncovalent BTK inhibitors, CAR T-cell therapy, or clinical trials, and hopefully this will lead to better outcomes.

So far, in the community setting, these therapies have not made as much of an impact yet as they're just kind of rolling out. And I think we see that here from this series of real-world retrospective data that show that outcomes are poorer after progression on noncovalent BTK inhibitor. We see that on the left in terms of median survival with further systemic therapy, even those patients who are able to get additional systemic therapy have a median survival of less than a year. And again, those patients who are not able to move on to systemic therapy post covalent BTKi, have a median survival of less than a month.

On the right, you can see median survival with a couple of different regimens that can be used here, the R-BAC regimen, which is rituximab, with bendamustine and ara-C did seem to have better survival than alternative systemic therapies in this real-world series, although remember that this is retrospective, so there's certainly issues around patient selection, with perhaps the fitter patients getting the chemoimmunotherapy-based treatment here.

So although these covalent BTK inhibitors have been an important step forward in the care of relapsed mental cell lymphoma, clearly more needs to be done in later lines of therapy. This is another retrospective study using claims data in the United States from 2015 to 2021 looking at nearly 700 patients with relapsed mantle cell lymphoma. As you can see here, most patients are getting chemoimmunotherapy in line one of therapy. You can see that these different squiggly lines are connecting patients to their next lines of therapy. So a lot of these patients who got chemotherapy-based treatment in the frontline setting, mostly in the purple there, got another round of chemotherapy in the relapsed setting, although quite a few also in line two got ibrutinib-based therapies. You can see that in the light blue. I think one of the challenges, though, especially outside of clinical trials and outside of academic centers, is that the majority of patients with mantle cell lymphoma are not receiving any third-line treatment, and you can see that illustrated on the right. So the yellow represents patients who got second-line therapy but then received no therapy after that. And this clearly demonstrates an unmet need for third-line care in mantle cell lymphoma.

So we'll dive now into the data on pirtobrutinib in mantle cell lymphoma, which are based largely on this trial called Bruin, which is a phase 1/2 study that included patients with relapsed/refractory B cell malignancies. We'll talk a little bit later about the results with the CLL patients, but here we'll focus on the 166 patients with relapsed/refractory mantle cell lymphoma, most of whom had previously had

a covalent BTK inhibitor, but 14 of them were covalent BTK inhibitor naïve. There was a phase 1 3+3 escalation portion of this study, and eventually a dose of 200 mg of pirtobrutinib daily was selected for further study. And you see the study endpoints listed on the right.

These are the baseline characteristics of the patients with mantle cell lymphoma on the BRUIN trial. The median age was in the range of 70, and you can see there was a male predominance, which is typical of mantle cell lymphoma. These patients generally had a good performance status and had a fair amount of lymph node bulk, with about 1/4 of patients having 5 cm or greater lymph nodes at time of study entry, and most patients having bone marrow involvement. Overall, the group had a median of three prior lines of therapy, and you can see those therapies listed in the top right. So most patients had had a prior BTK inhibitor, nearly everyone had had prior chemoimmunotherapy, and there were even about 1/3 of patients who had had some kind of transplant, either autologous or allogeneic, and a variety of other treatments, including CAR T-cell therapy.

Most of the patients on this study had progressed on their prior BTK inhibitor, about 14% had come off due to toxicity. You can see this group was fairly enriched for higher-risk TP53 mutation, which was seen in about 20% of patients, and the Ki-67 which is a rough idea of the aggressiveness of the disease, was elevated above 30% in about 30% of the patients. So here you can see the waterfall plot for lymph node change on pirtobrutinib in these mantle cell lymphoma patients. The overall response rate was 49%, including 16% of patients in complete remission. You can see in the dark blue color here, patients who had previously discontinued their covalent BTK inhibitor due to progressive disease. The lighter blue is patients who discontinued due to toxicity, and then the gray is not known. But I think you'll agree that you can see that there were certainly patients who discontinued due to progressive disease or toxicity who responded well to pirtobrutinib in the setting. And I'll highlight that the median time to first response was fairly quick, at about a median of 1.8 months.

Here you can see a forest plot to look to see if there were particular clinical or genetic predictors of overall response rate in these mantle cell lymphoma patients. And generally, I would say no. If you look at on the left side, MIPI score. Patients with high-risk MIPI did seem to have a little bit of a lower overall response rate, suggesting their disease is more aggressive. But on the right, you can see really no significant factors that predispose patients to have an inferior response. Interestingly, the patients who had prior toxicity from a covalent BTK inhibitor, all the way in the bottom right, those are the patients who had the highest overall response rate compared to patients who had actually progressed on their prior covalent BTK inhibitor.

What about durability? So for the patients who responded, the median duration of response was 21.6 months, which I think is quite good. However, many of the patients didn't respond. And so if you look at the median progression-free survival, it's more modest at 5.6 months. In the lower right, you can see that the overall survival was fairly favorable, median of close to 2 years. And I think that reflects the ability of pirtobrutinib to potentially bridge patients from being in a very sick position, perhaps where they can't tolerate cellular therapy, and perhaps using pirtobrutinib, for example, as a bridge to CAR T-cell therapy or even to allogeneic transplantation.

What about patients with traditionally high-risk mantle cell lymphoma? So I mentioned before, Ki-67 with a cut-point of about 30% can be helpful, and you do see those more indolent mantle cell lymphomas with less than 30% Ki-67 having a longer median progression-free survival, close to 20 months, compared to those patients with high Ki-67 where the median PFS was only about 5 months. On the right, similarly with TP53 status, you can see patients with unmutated TP53 had a somewhat longer median progression-free survival, close to 7 months, compared to those patients with mutated TP53 where it was 3.7 months.

This just focuses on that small group of patients, 14 patients in total. I think they have data on 12 here in terms of their response. And these are the patients who are covalent BTK inhibitor naïve. So clearly here you can see excellent duration of response, but also progression-free survival in the top right and overall survival in the bottom right. And actually, the median follow-up here is quite long; it's over 2 years. So high overall response rate here, 86% high CR rate, 43% and quite good durability, I think raising the question of whether pirtobrutinib should be explored further in the context of patients who have not yet had a covalent BTK inhibitor.

Okay, so let's change gears now and talk about CLL and noncovalent BTK inhibitors. One thing I like to highlight when talking about relapsed/refractory CLL these days is that we have an evolving patient population here. There are older patients who may have just had minimal prior therapy, like a CD20 antibody alone or chlorambucil, not that common these days. Also less common now is patients who have only previously had an effective chemoimmunotherapy regimen, like FCR or BR. There are patients out there, but increasingly patients now are being treated in the frontline setting with targeted therapies. So what we're starting to see more commonly now in the clinic is these lower three categories. So we have the patients who have previously been exposed to a covalent BTK inhibitor and came off due to an adverse event, or they progressed while on covalent BTK inhibitor therapy. We have patients who have had prior time-limited venetoclax and electively stopped therapy, but later relapsed. And then we have patients who have relapsed after a covalent BTK inhibitor and the BCL2 inhibitor, venetoclax; this is a so-called double refractory population, which we're starting to see more and more in the clinic. Unfortunately for these patients with double refractory CLL, the therapeutic options are quite limited, and the outcomes have been poorer. And this is because, you know, these patients tend to have very aggressive CLL, they've become

refractory to kind of our two main regimens that we use. And you can see this reflected on the right in this series where the median overall survival ranged from about 1 month to 6 months, depending on how many prior lines of therapy these patients had had. But, you know, clearly, these are very short numbers for CLL, a disease with a very long natural history.

This is another study from the group in Australia looking at their patients over the last decade, from 2011 to 2020. And they had 165 patients treated with either ven or a BTK inhibitor, 42 of these patients had been exposed to both drugs, but when they really narrowed it down to patients who were truly refractory to both drugs, that was only 18 patients. Nonetheless, I think this is still informative. As we see on the left, the whole cohort had a median overall survival of only 5 months, and it didn't matter whether patients had progressed with Richter transformation to DLBCL or just had progressive CLL, the median overall survival was statistically similar between those two groups. Similarly, on the right, you can see if patients were initially treated with a BTK inhibitor and then went to venetoclax or vice versa, the median survival was quite similar. No difference there, statistically.

So let's talk about nemtabrutinib. This is the other noncovalent BTK inhibitor, not yet FDA approved, but currently in phase 3 clinical trials. The bulk of the data that we have so far in this drug come from a study called BELLWAVE-001. This was a phase 1 study with an expansion. And this study looked at a variety of different doses of nemtabrutinib, and eventually settled on 65 mg as a daily dose going forward. So in the 57 patients treated at that dose, the overall response rate was 53%, and you can see similar response rates in cohort A, patients with CLL who had two or more prior lines of therapy including a covalent BTK inhibitor and had a C481S resistance mutation. And then cohort B was patients who had two or more prior lines of therapy and were intolerant to a BTK inhibitor and had no C4801S resistance mutation. You can see responses in both of these different subgroups.

Here you can see that so far, the progression-free survival is not too different. The median has been reached in cohort A at 15.7 months, but cohort B has not yet reached a median progression-free survival on nemtabrutinib. And then this just gives you a sense for the durability of clinical response on nemtabrutinib. It's, of course, as we expect, particularly good in cohort B, because these are patients who do not have resistance to prior BTK inhibitor. It is a bit shorter in cohort A, where the median PFS is about 14 months. But certainly, this is a very active drug in this very difficult to treat population. And you can see that also illustrated here with some updated data from this nemtabrutinib study, again, showing response rates in the range of about 40 to 60%, depending on the different cohort. And you can see that when they break this down by subgroups of patients who had had prior dual therapy with BTK and BCL2, patients with C481S mutated BTK, those with high-risk deletion 17p or unmutated IGHV, really, across the board, all these patients have consistent response. And these are mostly partial responses, as we expect with BTK inhibitors in CLL; we don't tend to see complete responses with any of the BTK inhibitors.

Now let's talk about pirtobrutinib in CLL. And this is the same slide I showed you before, the BRUIN phase 1/2 study. But now, instead of focusing on mantle cell, let's focus on the 317 patients with CLL/SLL included on the study. So they broke this group down into two groups. So the BCL2 inhibitor-naïve group has never previously been treated with venetoclax, that's 154 patients in the green. And then BCL2 inhibitor-exposed group who had prior venetoclax, that's the orangish color, 128 patients. So the median age in the CLL patients on the BRUIN study was in their late 60s, again with a male predominance, again with about a 30% or so rate of bulky lymph node disease at study entry. Median of four prior lines of therapy. Overall, five prior lines in the patients who are also exposed to a BCL2 inhibitor, and you can see in the lower left, all of these patients had prior BTK inhibitor, covalent, and most of these patients had prior chemoimmunotherapy, close to 1/2 of the patients did have prior BCL2 inhibitor with venetoclax. You can see in the top right that about 3/4 of the patients in this cohort had developed progressive disease on their prior BTK inhibitor, and about 1/4 had come off due to toxicity. The lower right gives you a sense for their mutational profile at study entry. So close to 40% of patients did have a BTK C481 resistance mutation when they started on pirtobrutinib. Another 7% or so had a mutation in PLC gamma 2, which is kinase just downstream of BTK, and when mutated, it also confers resistance to the covalent BTK inhibitors. In the lower right, you can also see that about 1/2 of the patients had high genetic risk CLL with either a deletion 17p or TP53 mutation, and 86% of the patients had the more aggressive IGHV unmutated form of CLL.

So here's the waterfall plot for the BRUIN study in CLL, again looking at lymph node decrease in individual patients. And as you see, nearly all patients had at least some reduction in lymphadenopathy. The overall response rate was close to 82% with a small number of patients achieving CR, but as expected, most patients with a PR. So here you can see the progression-free survival for the overall group of patients with covalent BTK inhibitor exposure in the past, median PFS here is 19.4 months. And when they break this down by prior exposure or not to a BCL2 inhibitor, you do see those BCL2 inhibitor-naïve patients on the left having a somewhat longer PFS, median close to 2 years, whereas on the right, it's those truly double exposed patients, post covalent BTKI, post BCL2 inhibitor, where the median PFS is a bit shorter at just under 16 months. Now, again, interestingly, overall survival here is quite good for this population. Remember what I showed you before, where the median overall survival in that Australian series was only 5 months. Here we're seeing a median overall survival not even reached yet, with a median follow-up of 29 months.

So I think this speaks to the power of pirtobrutinib on its own to induce response that can be reasonably durable, but again, also the potential to use pirtobrutinib as a bridge to other therapies, such as cellular therapies or clinical trials, can be a very useful drug in that context.

So we talked a lot about resistance to covalent BTK inhibitors. What do we know so far about resistance to the noncovalent BTK inhibitors? The most of what we know so far comes from data on pirtobrutinib from the patients on that BRUIN study. Remember on the left the C481 is the most common site of acquired resistance mutations for the covalent inhibitors. We've also seen mutations with the covalent inhibitors in the gatekeeper residue T474, and a mutation in L528, which can potentially make the kinase dead, or at least impaired. And so that's kind of what we know about the covalent mutations. On the right, we saw before how pirtobrutinib may be able to bind in a way that doesn't care about whether there are these mutations there. However, we've started to now see the emergence of resistance mutations to the noncovalent BTK inhibitors like pirtobrutinib. And again, data from the BRUIN study has been very informative here.

So genomic analysis was performed at the start of the study, so the profile was assessed of BTK mutations, and then in the 88 patients who have had acquired resistance, additional sequencing was performed at the time of progression to understand what the changes look like. In total, about 68% of the patients had acquired mutations at the time of progressive disease, 44% of them had acquired at least one BTK mutation of progressive disease, and the others had acquired other mutations in different genes that were not BTK. You can see on the right, the list of 138 acquired mutations there, but again, most of them were occurring in the BTK gene at a variety of different sites, suggesting that, you know, resistance to pirtobrutinib is also largely probably driven through mutations in BTK; it's just different mutations than the resistance patterns for the covalent BTK inhibitors.

And I think this slide illustrates that nicely. So this is a visualization of what I was just discussing, the baseline versus the progressive disease samples. The Y axis here is the variant allele fraction, so the size of the mutant clone. And on the left, what you're seeing is the BTK C481 mutational profile. So this is the classic C481S, for example, that patients get on covalent BTK inhibitors. And that's why, on the baseline, on that far left, you can see high levels, high path mutations in many patients. When these patients go on pirtobrutinib, for the most part, those mutations go down. So you see a lot more downfacing lines on the far left, suggesting the pirtobrutinib, as we've seen clinically, is active against the BTK C481S mutant. However, while on pirtobrutinib, you also see the gatekeeper mutation, BTK 474, as well as this kinase impaired mutation, L528W, and you can see them rising. So these mutations are at a very low level, if there at all, at baseline. But as patients progressed on pirtobrutinib, these T474 and L528W mutations become relevant.

So because we've seen the development of resistance already with pirtobrutinib after a couple of years, there's been interest in building on pirtobrutinib, since it's such an active drug, and actually developing combination regimens that may help to decrease the risks of resistance mutations. And so one such effort was built into the BRUIN study. This is an arm of this phase 1b study that looked at a couple of different regimens. One of them was pirtobrutinib in combination with venetoclax, that was looked at in about 15 patients. And the other was a triplet regimen of pirtobrutinib, venetoclax, and rituximab. So a total of about 25 patients between these two arms. And you can see that the primary endpoint here was safety, but secondary endpoints included the various efficacy endpoints, including undetectable, minimal residual disease.

Like the main BRUIN study, these patients were median age in their 60s, and you can see that in terms of prior lines of therapy, this was maybe a little bit less than heavily pretreated subgroup here, median of generally one to two prior lines of therapy. Most of these patients had a prior covalent BTK inhibitor, CD20 antibody, chemoimmunotherapy. But none of these patients had prior venetoclax, because that was an exclusion for these cohorts. Again, the majority of the patients had stopped their prior covalent BTK inhibitor due to progressive disease rather than toxicity, and about 40% of the patients in this cohort had BTK C481 resistance mutations at study entry. In the lower right, you can see that 26% of the patients actually had TP53 aberrations, so high-risk disease, and about 80% in total had IGHV unmutated CLL.

So despite this challenging population, on the left, you can see the waterfall plot with the sum of the product of the diameter. So all the patients had at least some reduction in lymphadenopathy. With the PV doublet, the overall response rate was 93%. When you added it in the rituximab, overall response rate 100%. And there were some CRs here, which is different from what we see with pirtobrutinib monotherapy. So for example, with PV, 7 of these 15 patients achieved CR, 3 of the 10 with PVR. And the changes in lymph node decrease were actually pretty similar amongst the BTK inhibitor-naïve patients and the BTK previously treated patients. These combinations were pretty rapid in terms of how quickly they induced response, so median time to best response was just 2.4 months. And at the time of this analysis, the median time on study was a little over 2 years.

So what about using MRD here to understand a little bit more about the dynamics of how quickly response is induced? So the graph on the left here is showing you individual patients in the different rows, and then on the X axis, the different cycles where MRD assessments were done. You can see that this was looking at a threshold of 10 to the -4 for MRD, so 1 in 10,000 cells. The top there is

the PV cohort. At the bottom is PVR. Blue is when there's still detectable MRD. And orange is when there's undetectable MRD. And you can see, for many patients, by the cycle 5 assessment, they'd already become undetectable for MRD. For some patients, it did take a little bit longer, but especially as you get out toward, say, a year and a half or so, nearly all of the patients have achieved undetectable MRD at that point. And at least so far, all but one of the patients has sustained undetectable MRD during subsequent MRD assessments, although I would say that longer follow-up here is needed. Here you get a sense for the PFS, PV is the green and PVR is the orange, and you can see excellent durability of the response here. PFS rate overall at 18 months was 87.5%, and at 24 months close to 80% still.

So in terms of ongoing phase 3 trials with pirtobrutinib right now in CLL, most of them have focused on the relapsed/refractory setting. We saw a press release fairly recently saying that the BRUIN CLL-321 study has read out and is positive. This is comparing pirtobrutinib to investigators choice of idela plus rituximab, or bendamustine and rituximab in the relapsed setting. There's also a registrational trial of the triplet, pirto, ven, and rituximab compared to the MURANO regimen, ven/rituximab. This is a large phase 3 trial that is fully accrued now, but we don't have data yet. There's another study in the relapsed setting comparing pirtobrutinib to bendamustine and rituximab in the frontline setting. And then on the right is a study that's kind of interesting because it has a mix of patients. So there's a cohort comparing pirtobrutinib to ibrutinib in the relapsed setting, and a cohort comparing pirtobrutinib to ibrutinib in the frontline setting. So I think all of these studies are going to be informative, hopefully will lead to, eventually a full approval for pirtobrutinib to make this drug more accessible for our patients.

Also, I'll just highlight an exciting study that's getting underway in Europe now, being led by the German CLL study group. And this is called CLL18. One of the reasons why I'm excited about this study is the comparator arm. So they're using the venetoclax/obinutuzumab as the comparator, which I think is going to be very informative compared to other studies that often use chemoimmunotherapy as the comparator. The experimental arms here are PV, pirtobrutinib and venetoclax, but arm B is fixed duration, so all patients get 15 months of therapy regardless of whether they achieve undetectable MRD or not. But then arm C is MRD guided, so patients can get 15 months, 24 months, or 36 months of therapy, depending on when they achieve undetectable MRD.

Primary endpoint of this study is planned to be progression-free survival. And to me, one of the really interesting aspects of this is going to be to see if, in a randomized study, they can demonstrate a benefit to an MRD-guided strategy over a fixed-duration strategy. It's not so obvious to me that it's going to be better, but if it is better, I think that really will help to justify the use of MRD in routine clinical practice to individualize therapy for particular patients.

All right, so let's change gears a little bit now and talk in some detail about the safety profile of the noncovalent BTK inhibitors. First, let's talk about the pirtobrutinib safety data in relapsed/refractory mantle cell lymphoma from the BRUIN study. At the time of the safety analysis that you see in the table on the right, the median time on treatment was just under 6 months. Only about 3% of patients had to discontinue pirtobrutinib due to treatment-related AEs. Similarly, only 5% of patients had to have dose reduction. Rates of treatment-related AEs were relatively low. You see some fatigue, diarrhea, and dyspnea, but grade 3 or higher levels are quite low in the 0 to 3% range. Infections were relatively modest, about 15% of patients 3.6% grade 3 or higher, and then some of the more classic BTK inhibitor type of toxicities were observed as low grade: arthralgias, hypertension, afib, bruising. But as you see on the far right, the grade 3 or higher toxicity rates were quite low. Similar table here, looking now at larger dataset, 282 patients with CLL treated in the relapsed setting with pirtobrutinib. And you can see very similarly some low-grade treatment-related AEs like neutropenia and contusion, but very low rates of grade 3 or higher toxicity; really, neutropenia is the one that stands out at about 15%. Again, in the lower right, some of the AEs of special interests, like hemorrhage, hypertension, afib, flutter, really kind of at the background rate of what you might expect in this older patient population.

Now, as we add in the venetoclax to pirtobrutinib, as I showed you, we see better efficacy. But what about safety? Well, in the initial dosing, there were no dose-limiting toxicities observed with this combination. There was only a need for a dose reduction of one patient with pirtobrutinib. There were a couple of cases of clinical tumor lysis syndrome related to the venetoclax escalation. Fortunately, both of these were reversible. One of them resolved spontaneously within 24 hours. The other was more serious and did require IV fluids and temporary dialysis, but that patient also recovered. And both of those two patients have now completed all 24 cycles of combination therapy. On the right, you can see the treatment-emergent AEs in the PV doublet patients, so just 15 patients here, but kind of a similar signal as what we saw before, neutropenia, diarrhea, kind of being the most common treatment-related AEs that are observed. And in the lower right, relatively low rates of cardiovascular toxicities like hypertension or atrial fibrillation.

When they added in the R, so now we're looking at the data for the triplet pirto, ven, and R, similarly, no DLTs. Very few patients needed dose reductions or dose continuations. And on the right, you can see, again, a favorable profile. You know, obviously when you add in rituximab, you do have some risk of infusion-related reactions. There were a couple of more serious infusion-related reactions in this study, so something to watch for. But again, in terms of cardiovascular signal and bleeding risks, relatively modest with this BTK

inhibitor.

Now, what about nemtabrutinib? So this was also rigorously studied in the BELLWAVE trial, 112 patients treated with 65 mg of nemtabrutinib. This included patients not just with CLL, but other relapsed B cell malignancies. One of the interesting toxicities of nemtabrutinib is dysgeusia, which pops up in about 20% of patients. Tends to be mild and reversible, but something to counsel patients about. We do see a neutrophil count decrease here in about 20% of patients, including 17% where it's grade 3 or higher. But really other than that, some mild hypertension and just other things to keep an eye on, but nothing that's too concerning.

So as we think about the key points on safety considerations for the noncovalent BTK inhibitors, just to highlight again, that pirtobrutinib is a selective noncovalent BTK inhibitor. The toxicity profile looks highly favorable. You do see some neutropenia as well as an infection risk, but those are really the most common grade 3 or higher toxicities observed. Nemtabrutinib, which is not yet FDA approved for any indication, is a little bit less selective than pirtobrutinib in terms of targeting BTK, but it's also quite well tolerated for the majority of patients. I highlighted that low-grade dysgeusia, which is worth counseling patients about, but otherwise it's a well-tolerated drug for most patients. Cardiovascular toxicities are still a common concern for all patients on BTK inhibitors. It does seem like the noncovalent BTK inhibitors have a more favorable safety profile cardiovascularly, but some of that might also just be that we don't have as much experience with them yet, so we'll see over time if that holds up. Certainly patients who are older and have a history of myocardial fibrosis, edema, or hypertension, or patients with pre-existing hypertension, they may need closer monitoring, they may have a higher risk of cardiovascular toxicities. And I just put in a reference here for an algorithm for monitoring and managing cardiovascular adverse events in patients on BTK inhibitors, a very helpful reference.

So in our final section here, we'll talk about patient selection and treatment sequencing for MCL and CLL, and we'll do this with a case-based methodology. Let's start with case number 1. This is a patient with relapsed/refractory mantle cell lymphoma. The patient was initially 53 years old, with no major comorbidities, and began to develop a relatively quickly progressing bulky lymphadenopathy. Was diagnosed with stage IV mantle cell lymphoma with a Ki-67 of 60% and unfortunately, a TP53 mutation. So this patient was treated with frontline BR and achieved a CR, and then went on to receive autologous stem cell transplant. Unfortunately, 1 year after transplant, this patient developed bulky lymphadenopathy again and needed to be started on zanubrutinib.

She's done well on zanubrutinib in a PR now for about 3 years, but has developed progressive lymphadenopathy again. You check with her, she's still taking her zanubrutinib, so she is, unfortunately progressing while on zanubrutinib. So you send off your panel to look for a mutational testing. But as that's cooking, how would you treat this patient now? Would you move to another covalent BTK inhibitor like acalabrutinib? Would you start CAR T-cell-based therapy with brexu-cel? Would you use pirtobrutinib? Choice D is all the above options would be reasonable. Choice E is either acalabrutinib or pirtobrutinib would be a reasonable option. And choice F is either brexu-cel or pirtobrutinib would be a reasonable option.

So I would argue that F here is the best answer, so brexu-cel or pirtobrutinib would be reasonable options. I think it depends a bit on how aggressive the patient wants to be. You know, in this case, this is a pretty young patient in her 50s, and has high-risk disease with TP53 aberration, high Ki-67 so although I would expect some response from pirtobrutinib, I'm not sure how long-lived it would be. So this might be a patient where I'd be considering going to brexu-cel as an initial option in the relapsed setting. And you could imagine an older patient where maybe brexu-cel toxicities may be challenging, and that's a patient where pirtobrutinib may be good to use first. So this highlights, I think, really, how we have to individualize therapy for our specific patients.

Since brexu-cel was one of the choices, I thought I'd just briefly review the data from ZUMA-2, updated and published in 2023. And really, just to highlight that CAR T has greatly improved the outcomes for our patients with relapsed/refractory mantle cell lymphoma, ZUMA-2 did have 68 such relapsed/refractory mantle cell lymphoma patients. And the median progression-free survival here is about 26 months. And you can see that patients who do achieve CR have a median PFS that's in the range of 4 years. So these responses can be very durable in mantle cell lymphoma relative to other therapies we have available. I would say over time we do see even that CR curve kind of drifting downward over time. So unlike DLBCL, as we got out sort of past 3 years or so and started to see that plateau on the curve as a curative potential for CAR T, I'm not sure that brexu-cel is going to be curative for most patients with mantle cell lymphoma, but certainly can provide durable benefit for many.

And it's reassuring as well that in the real-world setting, brexu-cel, now that it's been approved, seems to be performing pretty similarly to what I just showed you from ZUMA-2. Here with the real-world dataset, the overall response rate is 90%, including 78% CRs. And just to remind you, in the ZUMA analysis, overall response rate was 91% and CR rate was 68%, so looks very similar here in the real-world setting. On the right, you can see the estimates for duration of response, which also look quite good, especially for those patients who achieved CR in the range of about 2/3 of patients still responding after 12 months.

So when we have a patient like the one I presented in clinic, how do we decide between brexu-cel or pirtobrutinib? So I think some of

the practical things that I mentioned before, age of the patient, fitness, comorbidities, those can certainly factor in, what are their goals of care. But also, you know, there have been efforts now to try to compare across different trials using different methodologies to try to understand a little more of a scientific way how these treatments back up to each other. So this is one such example. This is a MAIC, which is a Matched-Adjusted Indirect Comparison, where basically they're taking data from two different studies, trying to align the variables of the baseline characteristics of the patients as much as possible, and then using that matched-adjusted algorithm to kind of try to compare apples to apples, as much as that's possible between two different studies. So by doing that here, you can see, in general, these treatments look fairly similar when it comes to overall response rate and CR rate. You can see there are some slight advantages favoring brexu-cel in terms of CR rate, certainly as we expect with the matched-adjusted analysis. And in the lower right, to my eye, these are tracking a little bit more on the side of brexu-cel, but some of these are not statistically significant in terms of progression-free survival and overall survival. So I think this type of analysis is somewhat helpful. But again, to me, with my patients, it's more about the individual patient, what their goals are, comorbidities, age, etc., all of that factors into this decision.

So now let's talk about a patient with relapsed/refractory CLL. This patient was 59 years old, had some hypertension, but no other medical conditions, and was diagnosed with Rai stage I CLL. Prognostic marker testing was done and showed normal FISH, but unmutated IGHV, and TP53 was wild-type. So this is sort of an intermediate aggressive CLL. It's not high-risk CLL, but it's also not the type of CLL that's likely to stay indolent forever.

So as you might predict from the unmutated IGHV, this patient, over the next 3 years, gradually developed cytopenias, developed some pretty bulky 4- to 5-cm palpable lymphadenopathy, and now at the age of 62, he meets iwCLL criteria for frontline treatment. So this patient goes on ibrutinib and stays in remission for about 8 years. So pretty typical story for ibrutinib. Tolerated it well. But now he's aged 70, and he's developing progressive bulky lymphadenopathy while on ibrutinib, which is certainly concerning. And unfortunately repeat genetic testing now reveals the high-risk TP53 mutation.

So given the following options, how would you treat them at this point? A, venetoclax-based treatment; B, pirtobrutinib; C, liso-cel; D, all of the above would be reasonable options; E, either a venetoclax-based treatment or pirtobrutinib would be the most reasonable options; Or F, either pirtobrutinib or liso-cel would be the most reasonable options.

So I think the best answer here is E. This is a patient who's had a BTK inhibitor but has not had venetoclax yet, so I'd be hesitant to jump into CAR T-cell therapy right away. It wouldn't be on-label anyway, so I probably couldn't get it paid for.

Venetoclax does have prospective data in this setting, post BTK inhibitor, so that would sort of be our more traditional choice of what to use next. However, as I showed you, from the BRUIN study, pirtobrutinib also has very good data, especially in this population that's only had one type of therapy, and not the double refractory, but kind of a single refractory population. So I think that also could be a great option. So I think either of these would be good.

These MAIC analyses have also been used in this context. So again, like with the mantle cell MAIC that I showed you, the idea is to match the baseline characteristic variables between two different studies. And this case, it's comparing prospective trial of venetoclax monotherapy to the BRUIN dataset for pirtobrutinib. And these treatments look pretty similar to me in terms of survival probability, those curves are largely overlapping. On the right, you can see toxicity profiles, which certainly do differ between the drugs. Tend to see more cytopenias, febrile neutropenia, infectious complications with the venetoclax. With pirtobrutinib, the toxicity profile does look quite favorable, even if you can see some of those toxicities. I think that this MAIC suggests that either approach is effective, they do have somewhat different side effect profiles, so that might also kind of help to individualize therapy for patients depending on their other medical issues.

Now, what about the data for liso-cel, the autologous CD19 CAR T-cell product in CLL? So these mainly come from the TRANSCEND 004 trial. These patients underwent classic lymphodepletion with fludarabine and cyclophosphamide. Then they were treated with one of two different dose levels of CAR T-cell therapy. So there was a 50 times 10 to the $6^{th}$, and 100 times 10 to the $6^{th}$. Then this dataset was reported out. So they prespecified an analysis, initially in the full study population treated at dose level 2. That's 87 patients. But then they had a particular focus on what's highlighted there in the orange in the top right, which is the double failure population, post BTK, post Venetoclax, treated at dose level 2. So that was 49 patients. And you see the CR rate in that group is 18%, the overall response rate was 43%, and about 63% of patients did achieve undetectable MRD in the blood.

Now interestingly, here you can see, whether looking at the full study population on the left or this double refractory population on the right, that the rate of CR is actually most predictive of the PFS, and so that's kind of the light blue curve on the left. You can see there was one late progression event after 30 months. On the right, you can see no progression or death in the patients who achieved a CR, and you can see that the patients who had a PR did also enjoy a median PFS in the range of 26 months. But if patients didn't respond, then the median PFS was quite short, at only about 3.7 months.

So as we wrap things up for this program, I wanted to really hit some of the key points here that hopefully will help you to integrate some of the new and emerging therapies in CLL and mantle cell lymphoma into your clinical practice.

First, noncovalent BTK inhibitors like pirtobrutinib and nemtabrutinib may provide benefit for patients who are progressing while on covalent BTK inhibitors like ibrutinib, acalabrutinib, or zanubrutinib. If you have younger, fit patients, particularly if they're in the double refractory setting, and they're eligible for a more definitive treatment, I do recommend thinking about referral for CAR T-cell therapy. As you saw, the safety profiles for these agents tend to vary widely. Some of them are very well tolerated, and some of them are more toxic. You know, in particular, the BTK inhibitors, especially the more selective ones, are quite well tolerated. Cellular therapy, although effective, is certainly more toxic with risks of cytokine release syndrome and neurologic events. We're lucky to have these options, but we do need to consider patients' comorbidities and disease status, and really try to optimize the most appropriate therapy for an individual patient. We also have to take into account shared decision-making and understanding the expectations of therapies and also what their preference is in terms of continuous versus time-limited therapy.

So hopefully you agree that although we've made a lot of progress in the treatment of relapsed/refractory CLL and mantle cell, there's still a lot of progress that can be made. There's a lot of unanswered questions. And I do encourage you to consider referring patients for clinical trials if there are any in your area. I do think that active participation in clinical trials really remains critical to help us to further optimize the outcome for patients with relapsed/refractory mantle cell lymphoma and CLL.

Thank you very much for your attention, and I hope you join us for another program soon.

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