Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/btki-breakthroughs-overcoming-treatment-resistance-in-cll-mcl/14825/

Released: 03/23/2023
Valid until: 03/23/2024
Time needed to complete: 60 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

BTKi Breakthroughs: Overcoming Treatment Resistance in CLL & MCL

Announcer:
Welcome to CME on ReachMD. This activity entitled: BTKI Breakthroughs: Overcoming Treatment Resistance in CLL and MCL, is provided by Forefront Collaborative, and this activity is supported by independent educational grant from Lilly. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

CHAPTER 1

Dr. Chang:
Hello, thank you for joining me today for this educational seminar discussing the role of Bruton's tyrosine kinase inhibitors in the management of chronic lymphocytic leukemia and mantle cell lymphoma. My name is Julie Chang. I'm Associate Professor of Medicine in the Department of Medicine and Division of Hematology, Medical Oncology, and Palliative Medicine at the University of Wisconsin School of Medicine and Public Health, and below are my disclosures.

So to begin, it's helpful to discuss the disease states of chronic lymphocytic leukemia and mantle cell lymphoma, which are the two disease states that we will be focusing on the role of BTK inhibitors. Both CLL and mantle cell lymphoma or chronic B cell lymphoproliferative disorders. They tend to occur in older age. So the median age at diagnosis is in the age - is in the 60s and 70s.

And there are many competing risks and potential complications associated with these underlying B cell lymphoproliferative disorders. We know that they are treatable, but they are ultimately not curable with any type of standard treatments. And the advanced age of patients at the time of diagnosis can certainly complicate the potential for complications related to underlying patient comorbidities. In addition, prior to about 10 years ago, the only standard treatment options we had available were cytotoxic chemotherapy with or without monoclonal antibodies. And this was particularly problematic in that as patients had more prior lines of chemotherapy, there was progressive immune dysfunction. In addition, there were issues with patients who had high-risk cytogenetics who were particularly resistant to durable response to chemotherapy. In addition, chemotherapy is very difficult, as patients have advanced age and other competing health risks.

So when BTK inhibitors became available, they were the first targeted agents approved for treatment of these histologies, and really significantly changed the landscape for therapy options in these disease settings. And initially, CLL was - CLL had a BTK inhibitor approved for treatment of relapse disease, and later it received a broad approval for any line of therapy. And currently, BTK inhibitors remain the standard treat - remain a standard treatment for relapsed mantle cell lymphoma.

So next, let's move on to module one, where we'll discuss the role of BTK inhibitors and its effect. So first, I'd like you to take a moment to answer this polling question which says: Which of the following statements is most accurate about BTK inhibitors?

Thank you very much for responding and hopefully, you will feel more confident about your answer as we move forward with this not this module.

So Bruton's tyrosine kinase inhibitor is a downstream protein complex with a major role in regulating signaling through the B cell receptor signaling pathway. And we know that one of the defects in mantle cell lymphoma and chronic lymphocytic leukemia is that

there's aberrant or chronic stimulation of B cell receptor signaling, and this results in abnormal proliferation, propagation, and increased pro-survival signals, and this can lead to abnormal prolonged survival of clonal B cells and abnormal expansion of those populations.

In addition, the downstream effects of BTK complex itself also can generate some increased proinflammatory cytokines, as well as generating several chemokine 's and other signaling pathways that direct B cell trafficking as well as tissue homing. The BTK inhibitors, the covalent BTK inhibitors have covalent, irreversible binding to BTK at cysteine residue 481. And this is a common feature of all of the covalent BTK inhibitors, which include ibrutinib, acalabrutinib, and zanubrutinib.

If we look at the different covalent BTK inhibitors, here, we can see that they share a common binding site but they have different molecular structures. And the molecular structures create different interactions with other adjacent kinases, leading to a variety of off-target effects, which we'll discuss in more detail.

When we're discussing the role of BTK inhibitors in treatment of CLL and mantle cell lymphoma, there are some important properties to understand. The first is which - the first of which is the phenomenon of lymphocyte redistribution. And this is an effect where when a patient is started on a BTK inhibitor, there's very rapid reduction in the total burden of lymphadenopathy, while there's simultaneously arise in the lymphocyte count. And that is illustrated to the graph on the right, where on the green line you can see rapid reduction in lymphadenopathy in the first 2 months of treatment, with a simultaneous rise in the lymphocyte count, followed by subsequent normalization of the lymphocyte count. And it's very important to recognize that this is a normal phenomenon which results from trafficking of nor - of malignant lymphocytes from lymph nodes into the peripheral blood, and this does not represent progression.

Another unique property of the BTK inhibitors is that patients can often have prolonged periods of disease control in the absence of a complete response. And this is very different than what had previously been observed with cytotoxic chemotherapy, where there's a very close correlation between the depth of remission and the duration of response. And we can see here from the Cooperative

Group trial, E1912, that compared standard FCR chemotherapy with ibrutinib and rituximab, that there was improvement in progression-free survival with ibrutinib and rituximab compared with chemotherapy, despite the fact that the complete response rate was significantly lower.

In addition, it's important to recognize that BTK inhibitors can have activity in higher-risk cytogenetic subtypes and other high-risk subtypes of disease. For example, a particularly challenging disease entity has been patients with 17p deletion disease in both CLL and mantle cell lymphoma. And we can see here from some of the initial studies with ibrutinib, that we see preserved rates of objective response rates even in patients with 17p deletion disease as well as 11q deletion disease, and that these responses are much more durable compared with traditional chemotherapy.

Another unique toxicity associated with BTK inhibitor is related to the off-target effects that result from the interaction with adjacent kinases near BTK. And in particular, I'll be focusing on the adverse side effects of bleeding and atrial fibrillation, as well as other cardiac effects. It's helpful to look at the package insert to compare the overall rates of bleeding and cardiac effects among the different covalent BTK inhibitors. We can see that with ibrutinib, the risk for any type of cardiac effect is reasonably high, primarily with hypertension, and that rates of grade 3 or higher atrial fibrillation and flutter is about 3.7%. We see that those rates of grade 3 or higher atrial fibrillation or flutter are lower at about 1% with acalabrutinib and zanubrutinib. And the way that major bleeding or hemorrhage is defined for each of the different drugs is slightly different. But we can see that the risk of major hemorrhage is about 4.2% with ibrutinib, and the risk may be slightly lower with acalabrutinib and zanubrutinib.

In conclusion, it's important to recognize that with covalent BTK inhibitors, there are very high response rates and durability of response even in the higher-risk subtypes of disease which make these particularly advantageous for management of these disease types. In addition, there can be some unique toxicities due to these off-target effects, particularly the bleeding and cardiac toxicities. And some of these issues are the basis for development of a newer generation of drugs that we'll be discussing more later on in the webinar, which is the non-covalent BTK inhibitors. And this is specifically to minimize some of these problematic off-target effects, as well as to allow for an option for therapy in the setting of disease that has become resistant to these covalent BTK inhibitors.

CHAPTER 2

Dr. Chang:
Moving on to the next module, next we will look at the current use of covalent BTK inhibitors in the treatment of CLL and mantle cell lymphoma.

So to review, there are three currently FDA approved covalent BTK inhibitors, acalabrutinib, ibrutinib, and zanubrutinib, all have been approved for mantle cell lymphoma that has received at least one prior line of therapy. These drugs also have approval for any line of therapy in CLL/small lymphocytic lymphoma.

I will briefly mention that there's a non-covalent BTK inhibitor, pirtobrutinib, that was recently FDA approved for mantle cell lymphoma having received at least two prior therapies, including a covalent BTK inhibitor. And we'll discuss this agent in much more detail later.

So first, let's look at a case of a patient with relapsed CLL. This is Mr. Hartson. He's a 72-year-old man who previously received bendamustine and rituximab 4 years previously, and now has disease progression. His medical history significant for ischemic cardiomyopathy, he has an ejection fraction of 45%, but no active heart failure, as well as hypertension and type 2 diabetes. His medicines include atorvastatin, glipizide, lisinopril, metformin, and metoprolol. So please take a moment to answer this question, which is: Would a BTK inhibitor be a good option for this patient?

Moving on to the next question, please take a moment to answer the question: Is there a preferred BTK inhibitor for a patient like Mr. Hartson?

Thank you for answering this question. We will now be discussing this case in more detail.

So looking at the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, specifically for treatment of relapsed chronic lymphocytic leukemia, you can see that there are several different options listed. I will highlight that the two most commonly utilized options are those containing a BTK inhibitor with or without a monoclonal antibody, or venetoclax, which is an oral BCL2 inhibitor in combination with a monoclonal antibody.

There have been multiple randomized trials that have compared BTK inhibitors with more standard therapy options for relapsed refractory disease, including chlorambucil, ofatumumab, as well as oral targeted agents such as idelalisib, or chemotherapy combinations, including bendamustine.

And we can see that in each of these circumstances, progression-free survival has strongly favored the use of a BTK inhibitor. And that also includes some long-term follow-up such as the 7-year data published with RESONATE-2, which clearly shows a significant improvement in progression-free survival with ibrutinib. We also see that the rates of atrial fibrillation and bleeding are very much in line with what I previously described in the package inserts for these agents.

So if we think about use of a BTK inhibitor in this patient, there are several clear reasons why this could be considered as an option. Certainly, the statistically significantly improved progression-free survival compared with other standard treatment agents, makes us a very appealing option. We know that compared with cytotoxic chemotherapy where there are high rates of neutropenia, infection, and other significant risk for grade 3 and higher toxicities, in comparison, BTK inhibitors have a generally better safety profile compared with traditional chemotherapy.

However, there are some negatives. One is clearly the indefinite nature of therapy when a BTK inhibitor is given as a single agent. These are drugs that need to be given until there is progression or intolerable toxicity. And throughout the period of dosing, patients are at risk for side effects. And this can be particularly problematic in patients who have cardiac histories or are on anticoagulation or antiplatelet agents that can increase the risk for bleeding.

The other question that we considered with this patient was whether or not there was a preferred BTK inhibitor for management of this patient. And I'd like to draw your attention to the results of the ALPINE trial which was recently presented at the American Society of Hematology meeting in 2022. And this was a phase 3 trial comparing ibrutinib versus zanubrutinib for patients with relapsed refractory CLL. And the study presentation included a 12-month planned interim analysis where the primary objective was objective response rate. And the overall response rate favored zanubrutinib, and this was statistically significant. And interestingly, the 12-month progression-free survival also favored zanubrutinib. In addition, during the period of reporting, there were significantly fewer rates of atrial fibrillation, cardiac events, major bleeding, or any adverse event leading to treatment discontinuation or death with zanubrutinib compared with ibrutinib. Therefore, I think zanubrutinib is a very attractive option to consider for many patients with relapsed refractory CLL, although it may be a bit premature to say that it is always the preferred BTK inhibitor in relapsed CLL.

Moving on to the next case. We will be discussing Mrs. Orozco, who is a 66-year-old woman with previously untreated CLL. She has been observed for about 2 years, but now has disease progression that needs therapy. Her medical history is significant for osteopenia and hypertension, which she's managed with alendronate and irbesartan. So the question is: What are the options for therapy? The patient does state to you that she's very interested in time-limited options. And are there any BTK-containing options that she could consider?

If we again look at the NCCN guidelines for treatment of previously untreated CLL, we can see that the two major categories are again a BTK inhibitor, or the oral BCL2 inhibitor, venetoclax, with or without a monoclonal antibody. In select circumstances, chemoimmunotherapy could be considered.

There have been multiple studies that have compared a BTK inhibitor with or without a monoclonal antibody given frontline compared

with more traditional standard options, primarily chemoimmunotherapy.

Here's a listing of some of these studies, and I would point out that these studies are very different in terms of the age of patients enrolled, some focusing more on younger populations, some focusing exclusively on older populations, as well as some diversity and whether or not high-risk subgroups such as those with the 17p or p53 mutation are permitted for enrollment. However, it is very clear in comparing all of these different regimens, that there is an advantage in each study in terms of progression-free survival, favoring ibrutinib or acalabrutinib compared with other standard treatment arms.

In addition, it's important to highlight that there is emerging data combining BTK inhibitors with venetoclax to allow fixed duration dosing. So we know that venetoclax induces very deep remissions of CLL, and can allow patients to receive therapy for 1 to 2 years, depending on the disease setting, and then take a break in treatment if they've achieved a deep enough remission. And so, combining a BTK inhibitor with venetoclax can allow for a BTK inhibitor to be given in a fixed duration setting. And if we look at the two larger phase 2 studies looking at this approach, CAPTIVATE and GLOW, where patients received 12 cycles or 12 months of combined therapy with ibrutinib and venetoclax, we see that a relatively early follow-up of about 2 years, that there are very promising rates of prolonged progression-free survival. So while this is still an emerging treatment that could be considered for patients, there certainly are data to justify in selected patients taking this approach.

And next, let's look at the case of Mr. Davis, who's a 75-year-old man with newly diagnosed mantle cell lymphoma who presented with bulky lymphadenopathy, splenomegaly, cytopenias, and fatigue. He has about 60% bone marrow involvement at the time of his staging. He has type 2 diabetes that is diet controlled, acid reflux disease, hypertension, but he is otherwise a very fit and active individual. He's a very well-educated person. He's a retired physics professor. And he's done a lot of reading about BTK inhibitors. And he has questions about whether or not he could receive a BTK inhibitor for treatment of his newly diagnosed mantle cell lymphoma.

So as I mentioned previously, all of the covalent BTK inhibitors do currently have an FDA indication for relapsed disease that has received at least one prior therapy.

And I've included here for your reference, the pivotal studies that led to that FDA approval.

I also just want to highlight for reference that that median progression-free survival when these covalent BTK inhibitors are used with mantle cell lymphoma, in general, is significantly shorter than what we see with use of these agents in chronic lymphocytic leukemia.

If we look at the NCCN guidelines for treatment of mantle cell lymphoma in the first-line setting, we can see that patients are very strictly risk stratified either into more intensive approaches with a goal of consolidated autologous stem cell transplant or non-intensive approaches without the plan for consolidative stem cell transplant, both groups of patients would be potentially eligible to receive maintenance rituximab after completing their induction therapy.

Although currently BTK inhibitors are primarily reserved for the treatment of relapsed mantle cell lymphoma, there were two recent studies that have looked at incorporating a BTK inhibitor into frontline treatment of mantle cell lymphoma. The first is the SHINE dataset which was presented in the *New England Journal of Medicine* last year in 2022. And this particular study looked at incorporating a BTK inhibitor with frontline bendamustine and rituximab induction in patients aged 65 and older. And I would point out that about 10% of the enrolled patients had evidence of a p53 mutation. Patients were randomized to either ibrutinib or placebo, and patients who achieved an objective response were then eligible to continue either their ibrutinib or placebo until the time of progression or unacceptable toxicity. And both groups were able to receive maintenance rituximab for up to 12 cycles of treatment.

This study had a long period of follow-up of about 7 years. And you can see in the top progression-free survival curve here, that median progression-free survival did favor ibrutinib-containing treatment arm with a statistically significant hazard ratio for disease progression and death. However, if you look at the lower overall survival curve, you can see that the outcomes appear very similar between the two groups. And this raises a question as to whether the advantage for a frontline BTK inhibitor was not seen on long-term follow up because patients in the placebo group were able to receive a BTK inhibitor at the time of relapse.

Another important study to describe is the TRIANGLE study which was presented at the American Society of Hematology meeting in 2022. And this study looked at incorporating a frontline BTK inhibitor for previously untreated mantle cell lymphoma. And this is a bit more of a complicated study, but this included younger patients aged 65 and younger who had a good performance status. The standard treatment arm in this study was induction chemotherapy with alternating R-CHOP and R-DHAP for six cycles followed by autologous stem cell transplant. The two experimental arms listed at the top include incorporation of ibrutinib into the induction setting of treatment as well as 2 years of maintenance ibrutinib after induction. And one of the treatment arms also included consolidative autologous stem cell transplant, but the other experimental arm did not include autologous stem cell transplant.

If we look at the failure-free survival curve from the study, which was the primary endpoint, we can see that the blue and red lines which

were the ibrutinib-containing experimental arms, had at least a trend towards improvement in failure-free survival compared with the standard treatment arm. There were somewhat complicated conclusions drawn from the study, which I don't want to confuse the issue by describing those in detail, but we can safely say that there is at least a trend towards improvement in failure-free survival with the addition of ibrutinib.

And if we look at the overall survival curves, we can see a very similar phenomenon to what we saw in the SHINE study, where there is not nearly as significant of a separation and the curves between the ibrutinib-containing arms and the non ibrutinib-containing standard treatment arm.

So if we draw some conclusions from the TRIANGLE study and the SHINE study, with the TRIANGLE study, again, there is some trend towards improvement in failure-free survival with the addition of ibrutinib. It is unclear if there will be an overall survival advantage. This data is too premature to say if ibrutinib does need to be incorporated into intensive frontline chemotherapy in younger patients, and it is definitely too premature to say that addition of a BTK inhibitor will negate the need for a consolidative stem cell transplant. In the SHINE study, we can draw very similar conclusions in that a frontline BTK inhibitor does improve progression-free survival; however, it is still unclear whether or not patients would do just as well with reserving a BTK inhibitor until the time of relapse. There's also some questions generated from the SHINE study as to whether new technologies such as minimal residual disease testing may better identify patients who would require indefinite maintenance therapy following induction therapy based on their risk for relapse. And lastly, both of these studies ultimately may generate some interesting data about whether high-risk groups, such as those with a p53 mutation, may be the group of patients ultimately most likely to benefit from frontline incorporation of a BTK inhibitor.

CHAPTER 3

Dr. Chang:
Moving on to the next module, we'll be discussing mechanisms of resistance to covalent BTK inhibitors as well as the development of the newer generation noncovalent BTK inhibitors.

When we look at mechanisms of resistance to BTK inhibitors, it's important to differentiate primary versus secondary resistance. The primary resistance implies that patients never had a response to a BTK inhibitor. And secondary resistance indicates that patients did have a response to BTK inhibitor and then subsequently had progression. It's also important to notice that another reason that patients have to discontinue BTK inhibitor therapy is not because of drug resistance, but because of in tolerability, particularly some of the off-target effects and toxicities, particularly bleeding and cardiac risks.

Primary resistance to covalent BTK inhibitor is very uncommon with chronic lymphocytic leukemia, but is much more common with mantle cell lymphoma. It could be that up to a third of cases of mantle cell lymphoma may never achieve an objective response to a BTK inhibitor. There are likely multiple mechanisms that contribute to this primary resistance. However, it is thought that possibly upregulation or mutations of other adjacent pathways allow for B cell receptor signaling to bypass BTK, which is the mechanism for resistance.

Secondary resistance is much more common. In about 80% of cases of chronic lymphocytic leukemia, this involves a mutation of the cysteine residue at position 481, which again is the binding site for BTK. In mantle cell lymphoma, this can represent a mechanism secondary resistance but is much less common than in CLL.

There are other more complex mechanisms of resistance. These include things such as genetic mutations, upregulation of other survival pathways and inhibitors, other genomic and epigenetic activation of some of the downstream signaling pathways, as well as clonal evolution or changes in the tumor microenvironment.

Please take a moment to answer the next polling question which is: Which statement is incorrect about the mechanisms of covalent BTK inhibitor resistance?

Thank you for answering that question. I hope that you were able to recognize that the incorrect answer is that most patients never develop BTK inhibitor resistance.

As I just mentioned, given enough time on therapy, most patients will develop resistance to BTK inhibitors.

Next, let's review the development of noncovalent BTK inhibitors, which are a new generation of BTK inhibitors that are able to inhibit the signaling through Bruton’s tyrosine kinase by a different mechanism.

One of the very unique features of these noncovalent BTK inhibitors is that they do not bind to the cysteine 481 site which all of the covalent BTK inhibitors do. And it's important to notice this because this is the primary mechanism of resistance in the majority of cases with CLL.

In addition, there are other important aspects of the noncovalent BTK inhibitor that helps improve efficacy and reduce potential for developing resistance to treatment. Firstly, there's highly selective binding to BTK inhibitor compared with other adjacent kinases. So this significantly reduces the potential for off-target effects and toxicities, making it more likely that patients will be able to tolerate treatment and not need to discontinue therapy for toxicity. We also see high levels of BTK inhibition even at trough drug levels, so we see very high levels of inhibition of BTK throughout the entire dosing interval. This may be particularly important for highly proliferative tumors. In addition, as we will review some of the data, we see high levels of clinical efficacy even in the setting of resistance to prior exposure to covalent BTK inhibitors.

There are currently two noncovalent BTK inhibitors in clinical development, pirtobrutinib and nemtabrutinib. Pirtobrutinib, as I briefly mentioned earlier, has just recently received approval in mantle cell lymphoma from the FDA in January of 2023. And the indication is for mantle cell lymphoma that has relapsed after at least two prior lines of therapy, including a prior BTK inhibitor. Another noncovalent BTK inhibitor in development is nemtabrutinib. It is important to notice that there are two other noncovalent BTK inhibitors, fenebrutinib and vecabrutinib, that were initially evaluated in this disease space, but ultimately further development was discontinued due to either lower than expected efficacy or toxicity concerns.

So focusing more on pirtobrutinib, this is a noncovalent BTK inhibitor that has reversible binding to BTK inhibitor. It's highly selective and it allows it to minimize some of the off-target effects and potential unintended toxicities. The datasets that lead to FDA approval was the BRUIN data which included multiple B cell histologies with several dose escalation and dose expansion cohorts. And we'll be focusing specifically on the CLL and mantle cell lymphoma cohort data.

Within CLL, the relapsed refractory CLL cohort of BRUIN included almost 300 patients. All patients had previously been treated with a BTK inhibitor, 75% had discontinued their BTK inhibitor therapy due to progression. You can see that this was a heavily pretreated patient population with a median of nine prior therapies. median age was 69. And you can see that about a third of patients had high-risk disease as defined by a 17p deletion or a TP53 mutation. And a majority of patients were able to receive the intended dose of 200 milligrams daily.

Looking at the outcomes in the CLL population of BRUIN, we can see that the overall response rate was very high at 74% in this heavily pretreated population. Almost all of them were partial remissions. And we can see that the 12-month estimated progression-free survival was 68%. And the 18-month estimated progression-free survival was 54%.

If we look at the grade 3 and higher treatment-related adverse events, we can see that neutropenia was the most common at 20%. But rates of events such as atrial fibrillation, flutter, and bleeding were significantly lower, and only 2% of patients required discontinuation of therapy due to treatment-related adverse side effects.

In addition, within the CLL cohort, there was a reporting of data based on several high-risk features, including age, whether or not patients had exposure to both a BTK inhibitor as well as a BCL2 inhibitor, presence of a 17p or p53 mutation as well as the presence of a mutation to the cysteine 481 residue. And we can see that in each of these high-risk patient populations, that the overall response rate and median progression-free survival is preserved in all of these groups.

Reviewing the mantle cell lymphoma cohort from the BRUIN study, we can see that this was a population that included 90 patients. Again, high-risk population, a median of three prior therapies, median age of 79, 82% of those patients had discontinued their prior covalent BTK inhibitor due to progression. And again, the majority of patients were able to receive the targeted dose of 200 milligrams daily.

The overall response rate was 58%. The majority of those were partial responses, including some responses and those with blastoid and pleomorphic histology which we know are higher-risk features. And we can see that both the 12- and 18-month estimated duration of response was over 50%.

If we look at the grade 3 and higher treatment-related adverse events, we can see that this profile is very similar to what had been observed in the CLL cohort treated with pirtobrutinib.

These data led to the FDA approval of pirtobrutinib in mantle cell lymphoma in January 2023. And as I mentioned, currently, the approval is for relapsed or refractory mantle cell lymphoma that has received at least two prior lines of systemic therapy including a covalent BTK inhibitor.

There are several ongoing studies in both CLL and mantle cell lymphoma with pirtobrutinib. So the top two boxes look at some ongoing studies of pirtobrutinib in frontline treatment of CLL and small lymphocytic lymphoma, comparing pirtobrutinib with bendamustine and rituximab chemotherapy, or pirtobrutinib compared with the covalent BTK inhibitor, ibrutinib.

And the bottom two boxes, it describes some ongoing studies in relapsed/refractory CLL and small lymphocytic lymphoma, looking at

combinations of pirtobrutinib with venetoclax, as well as a comparison of pirtobrutinib versus more traditional relapsed/refractory lines of therapy including bendamustine and rituximab, or rituximab with idelalisib.

There are some other interesting concepts with pirtobrutinib being investigated. So there is a time-limited combination of pirtobrutinib with venetoclax and obinutuzumab for previously untreated CLL/SLL as well as an interesting concept for pirtobrutinib consolidation after a limited course of therapy with venetoclax in patients at high risk for early relapse.

In mantle cell lymphoma, there are also some ongoing investigations with pirtobrutinib. A very important study ongoing in relapsed/refractory mantle cell lymphoma is a phase 3 trial comparing pirtobrutinib versus the investigator choice of covalent BTK inhibitor, either ibrutinib, acalabrutinib, or zanubrutinib. In addition, there's a phase 2 trial looking at a combination of pirtobrutinib and venetoclax in relapsed and refractory mantle cell lymphoma.

Another noncovalent BTK inhibitor under investigation is the agent nemtabrutinib. Some initial data reporting with this agent was from the BELLWAVE study, and this included a cohort of 57 patients with relapsed/refractory CLL/SLL. This was again a high-risk population, a median of four prior therapies, median age of 66. We can see that 95% of patients had previously received a covalent BTK inhibitor, and 42% had both a prior BTK inhibitor as well as a BCL2 inhibitor, such as venetoclax. And we can see that this was a high-risk subgroup, about a third of patients had either a 17p or p53 mutation.

In this initial data report, the overall response rate was 56%, primarily partial responses. And among those 32 responders, the median duration of response was quite promising. It was about 24 months. And if we look at the rate of grade 3 and higher treatment-related adverse side effects, it was very similar to what we had observed with the pirtobrutinib datasets.

Some ongoing studies with nemtabrutinib are listed below. The most important is probably the BELLWAVE study, which is a phase 3 trial comparing frontline treatment of CLL/SLL with either nemtabrutinib versus chemoimmunotherapy which is an investigator choice of FCR, or bendamustine and rituximab chemotherapy. In addition, there is a interesting novel drug combination trial with nemtabrutinib, in combination with the antibody drug conjugate, zilovertamab vedotin.

CHAPTER 4

Dr. Chang:
For our final module, we will be reviewing both the present and future development of covalent and noncovalent BTK inhibitors in the treatment of CLL and mantle cell lymphoma.

There are many clinically relevant issues that remain unanswered about the ideal role of both covalent and noncovalent BTK inhibitors in this disease setting. Probably the most clinically relevant question that as yet unanswered is whether or not patients should all receive a covalent BTK inhibitor up front, and reserve the use of a noncovalent BTK inhibitor at the time of recurrence. And it's important to note that the answer to this question may be different in different disease settings. So for example, we know that patients with mantle cell lymphoma do tend to have a shorter duration of benefit from covalent BTK inhibitors compared with CLL. So it is certainly feasible and possible that with additional testing, we would find that patients with mantle cell lymphoma may be better served by frontline therapy with a noncovalent BTK inhibitor.

Another very relevant question may be whether or not there is a role for mutation testing in making clinical decisions about uses of BTK inhibitors. As I mentioned previously, a majority of patients who develop secondary resistance to a BTK inhibitor will have a mutation of the cysteine 481 residue. And so, in patients who receive a BTK inhibitor frontline for treatment of their disease in some type of fixed duration regimen, it could be very practical and helpful from a clinical standpoint to know whether or not they have some type of acquired resistance prior to re-exposure with a covalent BTK inhibitor.

There are other relevant clinical questions that can be addressed in each individual disease setting. So in frontline chronic lymphocytic leukemia, it may be very helpful to look at whether or not a noncovalent BTK inhibitor may be more effective in improving progression-free survival when given in fixed duration regimens such as in combination with venetoclax. As we discussed in mantle cell lymphoma, the patients with p53 mutation do represent a particularly challenging disease group with higher rates of shorter progression-free survival and resistance to treatment. Could it be that incorporation of a noncovalent BTK inhibitor in frontline treatment may significantly improve outcomes? In the setting of relapsed and refractory CLL and mantle cell lymphoma, I already shared how mutation testing could ultimately have a role in better defining the use of a BTK inhibitor at the time of relapse. And in the research settings, the better toxicity profile of noncovalent BTK inhibitors may allow for more novel combinations of therapies with acceptable toxicity.

Please take a moment to answer the next polling question which is: Which statement is true regarding the current status of noncovalent BTK inhibitor use in the treatment of mantle cell lymphoma and chronic lymphocytic leukemia?

Thank you for answering that question. Hopefully, you were able to recognize that the lower rates of side effects with the noncovalent

BTK inhibitors may allow more patients to be eligible for BTK inhibitor treatment, and potentially tolerate treatment for longer.

In summary, covalent BTK inhibitors represented a very significant clinical advance in therapy of chronic lymphocytic leukemia and mantle cell lymphoma. It is important to have an understanding of the mechanism of action, and understand some of the clinical implications of that mechanism of action, including the phenomenon of lymphocyte redistribution, so that is not mistaken for early progression by clinicians. It's also important to understand that patients can have prolonged periods of benefit without achieving a complete response to treatment, as well as an understanding of some of the unique off-target effects of treatment. Particularly, the cardiac and bleeding risks need to be considered in the clinical management, particularly in patients with underlying cardiac risks, or patients who may already be receiving an antiplatelet agent or anticoagulants.

I also described some of the ways where covalent BTK inhibitors are being combined with agents such as venetoclax to allow more of a fixed duration regimen with use of a BTK inhibitor, rather than indefinite dosing until progression or in tolerability. And I describes some of the combinations of a BTK inhibitor with venetoclax in CLL. We also discuss some of the data from SHINE and TRIANGLE that looked at the use of a frontline BTK inhibitor in mantle cell lymphoma. And as I mentioned, these data are very compelling. But for example, data from the TRIANGLE does not yet support the routine use of the BTK inhibitor or that use of a BTK inhibitor can negate the need for consolidative transplant.

Noncovalent BTK inhibitors represent a very elegant model of novel drug design that are able to bypass one of the primary means of acquired drug resistance, specifically bypassing the very common occurrence of mutations at the cysteine 481 residue. And as previously mentioned, it is unclear if patients should initially receive covalent BTK inhibitors and then receive a noncovalent BTK inhibitor at the time of intolerance or resistance to a covalent agent. In addition, it will be very interesting to see whether or not mutation testing will gain a role in terms of selection of a covalent versus noncovalent BTK inhibitor.

In addition, the improved toxicity profile of a noncovalent BTK inhibitor will likely allow patients who are either intolerant to toxicities of a covalent BTK inhibitor or who have developed resistance to again achieve sustained periods of disease control.

And lastly, the recent approval of pirtobrutinib in mantle cell lymphoma represents a significant advance in that disease, and allows patients with very refractory disease and lack of other significant treatment options to have an acceptable treatment option with a favorable efficacy and toxicity profile.

Thank you very much for your participation in this educational webinar. I hope that you feel that there has been insight into the mechanism and clinical application of BTK inhibitors, and that you have clinically relevant information to use for patient management decisions. If you could now move on to the post-test for the final portion of the webinar.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Forefront Collaborative, and is supported by an independent educational grant from Lilly. To receive your free CME credit or to download this activity, go to reachmd.com/CME. Thank you for listening.