Advancements in the Management of Relapsed/Refractory B-Cell Malignancies – Integrating Recent Data into Practice to Improve Outcomes

CEC Podcast Transcript

Matthew S. Davids, MD, MMSc:

Hello, I'm Dr. Matthew Davids and on behalf of CEC Oncology, I'd like to welcome you to today's educational activity titled, *Advancements in the Management of Relapsed/Refractory B-Cell Malignancies – Integrating Recent Data into Practice to Improve Outcomes*. Today's program is supported by an independent educational grant from Lilly. Today's program is brought to you by CEC Oncology, an award-winning accredited provider of continuing education for clinicians worldwide. Today's activity may include discussions of products or devices that are not currently labeled for use by the U.S. Food and Drug Administration (FDA).

Again, I'm Matthew Davids. I'm an associate professor of medicine at Harvard Medical School, and leader of the Lymphoma Program at the Dana-Farber/Harvard Cancer Center. I'm also Director of Clinical Research in the Division of Lymphoma at Dana-Farber Cancer Institute in Boston. I'm very happy to be joined today by Amy Goodrich, who is a nurse practitioner at the Johns Hopkins Kimmel Cancer Center in Baltimore, Maryland. Here are our disclosures.

Our learning objectives for today are to implement novel treatment options for patients with relapsed/ refractory chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) based on the latest clinical trial data. To utilize an evidence-based approach for personalizing treatment for patients with relapsed/ refractory mantle cell lymphoma (MCL). And lastly, to develop team-based frameworks to oversee and address adverse events (AEs), prioritizing patient adherence and active engagement. Today we'll be focusing on these two diseases, CLL and MCL. You can see that CLL is more common than MCL with close to 21,000 new cases in 2023, whereas MCL had about 3,400 such cases. The average age of diagnosis is around 60 to 70 years for both diseases, and there is a male to female ratio of about two to three to one. If you add together the cases of CLL, SLL, and MCL, it comes to close to about a quarter of the total cases of non-Hodgkin lymphoma, as you see represented here in the pie chart.

So, as we go through the National Comprehensive Cancer Network (NCCN) guidelines for preferred recommendations, we see a lot of common themes between these two diseases. One difference though is that with CLL and SLL we almost never use chemoimmunotherapy anymore. You can see in the frontline setting we typically use either continuous treatment with a covalent Bruton tyrosine kinase (BTK) inhibitor or a time-limited combination of venetoclax plus obinutuzumab. Second-line treatment of CLL/SLL often uses the other agent that wasn't used in the frontline setting. And then in the relapsed/ refractory setting, we have the non-covalent BTK inhibitor pirtobrutinib and chimeric antigen receptor T-cell (CAR-T) therapy with liso-cel, which are both now approved.

In MCL there is still a role for chemoimmunotherapy in the frontline setting, particularly for younger, fit patients who historically have received high-dose therapy and autologous stem cell rescue. Although increasingly we've been using CD20 monoclonal antibody or BTK inhibitor maintenance and avoiding the auto transplant. In MCL we can also use covalent BTK inhibitors or lenalidomide with rituximab in the second-line setting. And then we have similar options again in the third-line setting and beyond with the non-covalent BTK inhibitor pirtobrutinib or CAR T-cell–based therapies.

The table at the bottom gives you a sense for the five different BTK inhibitors that we'll be discussing today, including the three approved covalent BTK inhibitors as well as the approved non-covalent inhibitor pirtobrutinib and nemtabrutinib, which is currently still in clinical development.

Let's start with the first portion of the program, which is focused on CLL. We're going to start with a patient case. Amy, this is a patient you've seen recently with double-refractory disease, so if you could please take us through the case and some of the data supporting your treatment recommendations, that would be great.

Amy L. Goodrich, RN, BSN, MSN, CRNP-AC:

Sure. This is a gentleman who was diagnosed with CLL at age 59. He had a history of hypertension and was otherwise healthy. He was diagnosed with Rai stage 1 disease and his prognostic markers showed normal fluorescence in situ hybridization (FISH), unmutated *IGHV* status and wild-type *TP53*. He was observed for about 3 years and gradually developed cytopenias and some bulkier adenopathy. At age 62 he needed frontline therapy for CLL. He was started on ibrutinib and quickly achieved a very good partial response, and he remained on ibrutinib in stable remission for about 8 years. Around age 70 he began developing bulky progressive adenopathy on ibrutinib. We repeated his genetic testing and the only change was he now has a *TP53* mutation.

As you described, we used the regimen we didn't use first line in second line, and he starts venetoclax with an anti-CD20 monoclonal antibody. He achieves a partial response and at the end of therapy has undetectable minimal residual disease, and he's got very small residual adenopathy that's positron emission tomography (PET) negative. So, he gets into a really good remission. After 2 years on venetoclax and his monoclonal antibody he develops steadily progressive lymph nodes. They're now bulky. How are we thinking about this patient?

He has double-refractory disease, and double-refractory disease is defined as of course double refractory to a BTK inhibitor, and venetoclax can be used in any combinations in any lines of therapy, just having had both of those patients must have progressed on a BTK inhibitor, so different from intolerance, so progression on therapy. And then there are three combinations of venetoclax refractoriness. They either can progress to be defined as double refractory, have progression on venetoclax, progression within 24 months of completing a venetoclax-based regimen, or being resistant to venetoclax retreatment. Again, it doesn't matter whether we're starting with a BTK and going to venetoclax or doing it the other way around, or even using a BTK with venetoclax as a therapy together. So, those are the combinations of how you can define double-refractory disease.

Why this matters is because these patients do not do well. This group looked at just under 400 patients who discontinued a covalent BTK inhibitor and a BCL-2 inhibitor. Looking at the survival probability, this is pretty dismal at 5.5 months. Now this data is from 2021, so we now have other options for these folks, which we are going to talk about. But, clearly this is where we still have a very big need for these patients who have been exposed to covalent BTK inhibitors and BCL-2 inhibitors. We need a much deeper toolbox of therapies than we have now. We're getting better, but we're not there, but we're doing better.

In this same vein, and this is from 2022, so again this is a few years old now. This group looked at patients who had had a BTK inhibitor, a covalent BTK inhibitor and venetoclax, so a double-refractory group, and looked at folks who got CAR-T. If you look at this and allotransplant, and we're going to go through these, but if you look at the numbers of patients treated, these are relatively small numbers of patients. But, nonetheless, those who got CAR-T in a double-refractory state had an overall response rate of 85%, but median progression-free survival

(PFS) is pretty short at 4 months. Allotransplant, again, had a good overall response rate at 76.5%, but only 11 months PFS.

Where the data look best is this non-covalent BTK inhibitor, and that was most typically pirtobrutinib, but 75% overall response rate. At 9 months, median follow-ups are the longest median follow-up in the data set, the PFS not yet reached. Then if you look at our PI3 kinase inhibitor group and chemoimmunotherapy group, those overall response rates are quite low, 40% and 31%, with median PFS of 5 and 3 months, respectively. So, very short responses with these regimens.

This group looked at subsequent lines of therapy doing electronic medical record retrospective review starting in 2016, and the data cutoff was 2003. They looked at patients who had CLL. The data suggested that patients who received a first-line covalent BTK inhibitor, followed by a BCL-2 inhibitor with an anti-CD20 monoclonal antibody, had the greatest overall survival benefit. But, when they looked at what patients were getting, very few patients had received those two lines of therapy sequentially.

First and second line, there was still a lot of chemoimmunotherapy being given. There was still a lot of single-agent anti-CD20 monoclonal antibodies being given. It was somewhere around 30% of patients who actually received a first-line covalent BTK followed by a BCL-2 with a monoclonal antibody. And then, just to point out, our novel treatments that we'll be talking about were largely unavailable to these patients because of the data cut off. So, where do we stand with double-refractory therapy for double-refractory disease? Matt, do you want to talk about how you treat your double-refractory folks?

Matthew S. Davids, MD, MMSc:

Yes, so this is a growing problem. We're seeing more and more of these patients in the clinic and unfortunately there are few good options. We've seen historically that the median time to discontinuation of the immediate subsequent line of therapy in these double-refractory patients is in the range of about 5 ½ months, and that's time to subsequent line of therapy or death. So, these are patients who often have very aggressive disease. We've seen novel mutations in BCL-2, for example, in the venetoclax-resistant patients. We know about the *BTK/PLC gamma 2* mutations in patients resistant to ibrutinib and the other covalent BTK inhibitors. So, a challenging population, but happy to say that there are some promising options that are being explored now.

We'll talk about the idea of venetoclax retreatment for patients who previously had a time-limited course of venetoclax, and we'll talk about the non-covalent BTK inhibitors, CAR T-cell therapy, and then other targeted therapies in development.

Let's start with venetoclax-based re-treatment. Is this an option for our patients? Well, there are accumulating data that in fact, yes, this could be an option. Most of these are retrospective data. For example, this study that was a real-world collaboration but also included some patients from clinical trials. These were patients who had been treated with a venetoclax-based regimen once, which they called VEN1 in this analysis, and then went on to subsequently receive a second venetoclax-based therapy in a later line. You can see the median age of these patients is pretty young at the time of diagnosis in their mid-50s, but at the time of their first venetoclax, mid-60s. Male predominance as usual. Median of two prior lines of therapy in this analysis. You can see it's a pretty heavily pre-treated group and also genetically enriched for high-risk disease, with at least a quarter of the patients having deletion 17p and over 80% having IGHV unmutated disease.

It was a relatively small group of about 46 patients, you can see on the left side there, and the overall response rate to their first venetoclax therapy was very high, close to 90% when you add up the partial responses (PRs) and the complete responses (CRs). Then you see that the overall response rate to the second round of venetoclax is a bit lower. In the BTK inhibitor–exposed patients, it's 56%. So, still the majority are responding but not as robustly as in the first time they got venetoclax. On the right you can see that median PFS comes out at around 2 years or so from that second course of venetoclax.

We certainly do need prospective data sets here. We're actually currently running a study called ReVenG (Re-treatment with VenG), with VenG being venetoclax and GA101 (GA101 is the old name for obinutuzumab) to look at this prospectively. But, I do think based on retrospective data sets like this, it does suggest that we can see a high overall response rate and reasonable durability with venetoclax-based re-treatment, even in this double-exposed or double-refractory population.

What about the non-covalent BTK inhibitors? I'll just briefly mention nemtabrutinib, because it's not yet FDA approved, but I think it's important to know that this is a promising agent that is now in late phases of clinical development. What I'm showing you here are some data from the phase 1/2 open-label study of nemtabrutinib, which focused on patients with double-refractory disease. Cohort A included patients with two or more prior lines of therapy, including a covalent BTK inhibitor, who were documented to have a BTK C481 resistance mutation. Cohort B was a similar population but did include patients who are intolerant to a covalent BTK inhibitor or those without a *C481* mutation.

You can see that the PFS curves here I think overall look promising, I would say particularly in those BTK-mutated patients, lighter green where the median PFS was in the range of 26 months. Those patients who were completely double refractory, the prior BTK and BCL-2, had a median PFS that was significantly shorter at about 10 months. So, I think it does suggest that this is an active drug and we're eager to see more data with it, and phase 3 data are on the way.

We have more data for pirtobrutinib, which is the non-covalent BTK inhibitor that has received accelerated approval already in the relapsed/refractory CLL population with at least two prior lines of therapy, including a covalent BTK inhibitor. And that approval was based on the BRUIN study, a phase 1/2 open-label trial of pirtobrutinib monotherapy where they looked at close to 250 patients with CLL who were pretty heavily pretreated with a median of three prior lines of therapy, and they all had had prior covalent BTK inhibitor. Most of them had had prior chemoimmunotherapy, and just over 40% of these patients had also had prior venetoclax. You can see that close to 40% of the patients had TP53 aberration and 85% had unmutated IGHV, so genetically a very high-risk group. Nearly 40% had a resistance mutation in BTK such as C481. About a quarter of the patients in the BRUIN study had discontinued their prior BTK inhibitor due to toxicity and about three-quarters due to progression.

Here you can see the PFS for the patients in the BRUIN study were treated with pirtobrutinib, which does look promising, with a median PFS reached at around 19 months or so, 19.6 months in the previous covalent BTK inhibitor–treated population. If you look at the subset of patients who had a prior covalent BTK inhibitor and venetoclax, it's about 100 patients. The median PFS is just under 17 months in that group. And you're seeing response rates here in the 80% range, again, in a very heavily pre-treated group that's difficult to treat.

So, we just reviewed two options. We talked about venetoclax-based treatment post covalent BTK inhibitor, and we talked about pirtobrutinib. How do these two approaches stack up? The short answer is we don't really know based on any kind of prospective randomized data. And this I think is a good scenario to think about, a

matching-adjusted indirect comparison (MAIC) analysis, which tries to look across different studies and match the pre-baseline characteristics of the patients as much as possible to try to see how these therapies may compare. There are a lot of caveats to this type of analysis. The patient populations are different. Some of these data sets come from different eras. But, nonetheless, I think it does give you a sense that either of these options can be effective in the BTK inhibitor pre-treated population. To me, these numbers look pretty similar, suggesting that either can really be a good approach for our patients. We'll await additional larger and comparative data sets to understand the nuances of which regimen may be better for which patients.

A newer data set that just came out at the ASH 2024 meeting is the BRUIN CLL-321 trial, which is the registrational trial for pirtobrutinib in the relapsed/refractory setting. This is a phase 3 study comparing continuous pirtobrutinib monotherapy to investigator's choice of a standard 6-month course of bendamustine and rituximab or to continuous treatment with the PI3 kinase delta inhibitor idelalisib given with an initial 6-month combination with rituximab. The primary outcome for this study is PFS. We saw that in general the pirtobrutinib regimen was very well tolerated. You do see some cytopenias and infectious complications, as is true for any regimen in CLL, but overall the rates of discontinuation due to treatment-related AEs as well as dose reductions were significantly lower with the pirtobrutinib arm compared to the investigator's choice arm.

Interestingly, also, even though it's a BTK inhibitor, there was very low rate of cardiovascular side effects with pirtobrutinib in this BRUIN 321 study; for example, 2.6% atrial fibrillation (AFib) flutter, 6% hypertension, and a low rate of bleeding issues. In the lower left you can see in the PFS comparison that pirtobrutinib was superior to idelalisib rituximab or bendamustine and rituximab, both in terms of PFS and time to next treatment. And, in fact, the median time to next treatment was a little over 2 years in that pirtobrutinib arm, suggesting that these responses can be durable. The overall survival analysis is not yet mature for this study.

So, rather than using pirtobrutinib or venetoclax in sequence, what about the idea of combination pirtobrutinib-venetoclax? This is being explored in a number of different studies. We've seen data from this phase 1B trial of pirtobrutinib-venetoclax (PV) in 15 patients, or pirtobrutinib-venetoclax-rituximab (PVR) in 10 patients with a 25-cycle regimen. Again, a heavily pre-treated group with a median of two prior therapies, nearly 70% with covalent BTK inhibitor exposure and close to 40% with BTK-resistant mutations. Again, the majority of the patients in this study here had progressed on their covalent BTK inhibitor, and nonetheless you see 93%-100% of the patients responding here. You do see some CRs as well as PRs. We don't know as much yet about the durability of these responses, but it certainly does suggest that pirtobrutinib and venetoclax can be a very potent combination even in this post-covalent BTK inhibitor setting. And this was also a very well tolerated combination. I'll highlight also that pirtobrutinib-venetoclax is now being explored in the frontline setting in trials that are getting underway, such as the CLL-18 study in Europe.

I also mentioned that we have CAR T-cell therapy approved for CLL, and the product here is liso-cel. This is the CD19-directed autologous CAR-T product. The data here supporting it in CLL come from this study, TRANSCEND CLL 004. These were relapsed/refractory CLL or SLL patients with at least two prior lines of therapy. They all had prior covalent BTK inhibitor–based therapy, and then many of these patients also had prior venetoclax. You can see the typical schema here for a CAR T-cell–based study where patients underwent screening and then harvesting with lymphodepletion and then subsequent re-infusion of the cells. Interestingly, there were cohorts here that had combination of liso-cel with venetoclax. We haven't seen those data yet. And then liso-cel with ibrutinib, and we've seen some data from that cohort now as well. The primary endpoint of this study is the rate of CR-CRi.

Here you can see the data from liso-cel monotherapy, which was published in *The Lancet* in 2023. Forty-nine patients in this study had prior venetoclax and covalent BTK inhibitor exposure and were treated at dose level two of CAR T-cells here. The overall response rate was 43%, but the primary endpoint was a bit lower. The rate of independent review committee (IRC)-assessed CR/CRi was 18%. You can see the undetectable minimal residual disease (MRD) rate in the marrow was close to 60%. These patients were having deep responses but, overall, this was a shorter PFS than many of us had expected. You can see that here with the PFS curves. These curves are brought down by the patients who didn't respond and there were quite a few of them. In the non-responders, the median PFS was only 3.7 months. On the other hand, in the small number of patients who did achieve CR/CRi, you can see that top light blue curve, the median has not been reached, and in fact there were no progression events in the first 2 years in those patients who achieved CR. There does seem to be a benefit to achieving at least a PR. Median PFS there was just under 27 months and, overall, the median PFS is in the range of about 18 months. On the right, you can see the overall survival, with a median follow-up of about 2 years. Again, similar trends. You don't see any of the patients who achieved CR having died. You do see a benefit to PR and the median overall survival is about 43 months, so it's not bad considering that this is a very difficult-to-treat population. That being said, for patients who don't achieve a CR, it can be very challenging to have a durable response.

There have been a number of efforts underway to try to enhance the activity of liso-cel, and we've now seen some initial data from this liso-cel plus ibrutinib cohort that was presented at the ASH meeting in 2024. This was 56 patients who were treated with ibrutinib throughout that period that I showed you of initiation and lymphodepletion and the subsequent period of engraftment of the CAR T-cell product, and they received ibrutinib for about 6 months after that CAR T-cell reinfusion. Interestingly, here the median has not been reached in terms of overall survival, median PFS in the range of about 31 months. You can see that the CR rate is 45%, which looks significantly higher than that 18% we saw with liso-cel monotherapy. Similarly, the overall response rate here is high at 86%, and 84% of patients did achieve undetectable MRD in the marrow.

It's difficult to compare across these cohorts. I would say that this cohort with ibrutinib was a little bit less heavily pretreated than the liso-cel monotherapy cohort. But I think there really might be something to this data set, both in terms of reducing the CLL disease burden with the BTK inhibitor but also potentially some of the immunomodulatory effects of BTK inhibition. I think this is certainly inspiring for developing larger data sets of combination BTK inhibitor plus liso-cel.

So, let's get back to our case. One of the major considerations we have in treatment decision-making for patients in later lines of therapy is the impact of AEs. Amy, I want to bring you back in here and see if you can help walk us through the range of AEs that patients who are receiving BTK inhibitors might experience and how those are managed in the clinical setting.

Amy L. Goodrich, RN, BSN, MSN, CRNP-AC:

Sure. To look at common or problematic BTK inhibitor toxicities, you have already alluded, Matt, to the fact that cytopenias and infections are just a way of life with these patient populations, and I put fatigue in that category as well. Some of the toxicities are from off-target effects, and so as we now have first-, second-, and third-generation BTK inhibitors, each generation has fewer off-target effects and are generally more well tolerated and have lower incidences of some of these toxicities. One of the biggest problematic off-target effects is epidermal growth factor receptor (EGFR), which all those of you who see solid tumors you know are responsible

for arthralgias, diarrhea, rashes, and skin changes. And those are definitely seen with BTK inhibitors because of those EGFR off-target effects.

Some of the cardiac events are not as well understood in terms of the etiology, but they include very rarely ventricular arrhythmias and relatively infrequently AFib and AFlutter. Hypertension can be seen, and that is the one toxicity that becomes more prevalent with time. The others either plateau or become better with time. And then bleeding is an issue that we will talk about in a few slides here, but this is just a CliffsNotes version of the toxicities that are most problematic or common.

In terms of serious AEs, although low-level bleeding is very common with this disease, hemorrhage can be seen, AFib, AFlutter, and we're going to talk about this later. But it is really risk factors that are common to everyone, older folks, males, all sorts of cardiovascular diagnoses such as AFib, hypertension, hyperlipidemia, pre-existing cardiac disease. This is not special to the CLL population. This is in the general population, things that put folks at a higher risk of AFib or AFlutter. We talked about infections. Those can be serious, including opportunistic infections, and those cytopenias can be more severe. And then we're always worried about second primary malignancies. If you look at the data on our four approved BTK inhibitors, skin cancers and non-melanoma skin cancers are the most prevalent. Solid tumors are definitely seen as well but there's not a pattern to those. They're all over the solid tumors that are seen. It's skin cancer that tends to be the most common.

Another common side effect, which occurs in up to 50% of patients depending which BTK inhibitor is being used, is lymphocytosis, and this is due to lymphocyte redistribution. What happens is as a patient starts these therapies, nodes and spleens will decrease and those lymphocytes push out into the peripheral blood, and so you will see lymphocytosis. This typically peaks early at the first month or two. It's typically a slow decline downward. There are patients for whom the lymphocytosis never resolves and it doesn't affect outcomes, it doesn't mean anything. It's not prognostic of any outcome. It really does not require any specific management, even when it is persistent, as long as you're seeing those nodes in the spleen and other objective nodal masses decreasing, the lymphocytosis is just something that we have to ride out and it may or may not improve. But it's definitely something that patients need to be aware of because this is really disturbing, especially to those folks who have 10 years of Excel spreadsheets of their lymphocyte counts. This is something they need to be ready for.

Bleeding, which we've talked about, and typically is mild for grade 1 or 2 bleeding, you can hold. You don't necessarily have to hold. You can continue to monitor. You've got to tailor it to the patient. Grade 3 or above you're going to hold. You can consider transfusing platelets and then you can dose reduce once bleeding resolves. If you're using a first-generation, you can move to a second-generation as well if patients have significant bleeding. And then one of the most important teaching points is holding for procedures, holding 3 days before and after minor procedures, 7 days before and after major procedures because of that bleeding risk.

AFib, AFlutter, and like I spoke about, this is a relatively low-volume problem, about 10% in the RESONATE-2 trial with ibrutinib. The time to onset is just under 3 months, but this can really occur at any point in time. In addition to there being no special CLL-related risk factors, there's really not special management in terms of what you do to control the AFib. Certainly cardiology should get involved if the CHA2DS2VASc score is low; you can continue the BTK inhibitor at the current dose with using rate and rhythm control. Of course be aware of drug-drug interactions and try to choose beta blockers to avoid those drug-drug interactions. And then for higher CHA2DS2VASc scores, hold the BTK inhibitor, considering alternative therapy at that point. Then if you do need

to anticoagulate, really try to avoid warfarin and use direct oral anticoagulants or low-molecular-weight heparin; things with shorter half-lives are preferable.

And then there are other issues. Diarrhea is common. Just using over-the-counter antidiarrheals is typically a good approach. Headaches are pretty classic with acalabrutinib and it's usually self-limited. Within the first few months they come and go, and it's acetaminophen and caffeine that tend to do the best job and of course avoiding nonsteroidal anti-inflammatory drugs (NSAIDs) because of that bleeding risk. Hypertension, again, is the one issue that does tend to be more prevalent as time goes on, so we're monitoring for treatment-emergent hypertension and we're managing with antihypertensives, largely dependent upon other comorbidities. And then just know that when the BTK inhibitor therapy is stopped, it is very likely that the patients are going to be able to reduce or come off those antihypertensives.

We talked about infections. There is no blanket prophylaxis. You really are looking at the patient in front of you. What's their treatment history? What is their infection history? And you are tailoring any prophylaxis to the patient. Arthralgias and myalgias tend to be mild but can be some of the most problematic issues to deal with. These are very subjective. They may require dose reduction, dose interruption, sometimes a pulse of steroids, and, again, acetaminophen. These can be some of the most frustrating issues to try to get a handle on. Nausea. Antiemetics tend to do a good job if it's daily dosing, and taking at night helps. We talked about those cytopenias. I follow the package insert. For neutropenia, patients may require growth factor. You can dose interrupt. Same for thrombocytopenia. And then rashes, use topical steroids, oral antihistamines. There's really no specific management of these issues. This is really in line with a lot of drugs that we're giving and managing those the same way.

And in looking at, again, the matched indirect comparison of side effects, venetoclax versus pirtobrutinib, because, again, this is where we're, once a patient progresses through a covalent BTK inhibitor, are we giving venetoclax? Are we giving pirtobrutinib? Looking at those toxicities, you can see anemia is higher in the venetoclax group, about 28% versus 5% in the pirtobrutinib group. Febrile neutropenia is also higher in venetoclax. Neutropenia is higher in venetoclax as is thrombocytopenia. Pneumonia is in the unweighted pirtobrutinib group and is pretty similar to venetoclax. And then treatment discontinuations due to AEs are also, again, in the unweighted pirtobrutinib group pretty similar. So, in general as a blanket, it appears that pirtobrutinib is more well tolerated than venetoclax. But, again, this is not head to head. This is matched adjusted in direct comparisons.

Then looking at CAR-T, liso-cel. Looking at cytokine release syndrome (CRS), 85% of patients will be expected to develop CRS. As you can see, the majority are grade 1 and 2, only 8% is grade 3, and there was no grade 4 seen. And if you go to the grid at the bottom, median time to onset is 4 days, and the median time to resolution is about 6 days. Then for our neurotoxicities, only 45% of patients can be expected to have those. There is a little higher incidence of grade 3 at 18%, but the majority are grade 1 and 2. Then there was a 1% grade 4 incidence, and that happens about 7 days into the therapy and lasts about 7 days. If you look at the bottom, of those hundred patients, 82 required steroids and/or tocilizumab for management of CRS or neurotoxicity.

Then our other AEs are pretty typical for CAR-T therapy: cytopenias, infections, hypogammaglobulinemia, tumor lysis syndrome on that second primary malignancy issue, and then macrophage activation syndrome. In looking at deaths, there was really only one death directly related to the liso-cel, which was a macrophage activation syndrome death; the others were considered unrelated. And you can see respiratory failure, sepsis, and different infections there.

So, let's jump back to our case. Here we're having to decide what to do after covalent BTK and venetoclax failures. Matt, how do prior AEs affect your choice of therapy? How do expected AEs affect your choice of therapy?

Matthew S. Davids, MD, MMSc:

Thanks, Amy. These are clearly important factors as we counsel patients about the next line of therapy. A lot of these BTK inhibitor–related toxicities are class effects, I would say particularly bleeding issues. So, if someone's had a very serious bleeding issue on a BTK inhibitor, I'm probably not going to prioritize a BTK inhibitor in a later line of therapy unless I'm really out of other options. On the other hand, if I had a patient who had some mild arthralgias with a BTK inhibitor, I'd certainly be happy to try a different BTK inhibitor in the next line of therapy.

It's a similar approach with venetoclax. If I had a patient who really struggled with neutropenia and infections on their first-line venetoclax and they've gone through a covalent BTK inhibitor, I may not want to re-treat them with venetoclax as the next option. I may think about a non-covalent BTK inhibitor. On the other hand, if I had a patient who did great with frontline venetoclax, had a very long initial remission and then now is in the third-line setting, that could be a great patient to go back to venetoclax. So, I think it really depends on the type of toxicity, the severity of the toxicity, and these definitely impact our recommendations.

So, let's go back and recap where we're at with our patient here. Remember this is initially a 62-year-old man who was on ibrutinib for about 8 years and got a great response from that, now age 70 and has TP53 aberrant CLL. He goes on to venetoclax for a couple of years but now is progressing. So, what would I recommend for this patient? I would say this is potentially a good patient for CAR-T. This patient is still early 70s and pretty fit. Maybe you'd get a durable response. But on the other hand, we saw only an 18% CR rate with liso-cel and you really need to get to CR in order to be able to achieve durable response. So, I've started having these conversations with patients. I would say most of them so far have been choosing pirtobrutinib, which I think is also a great option, certainly easy to start, well tolerated, and high likelihood of helping. And this is a patient where I might start with pirtobrutinib and then be prepared to move to liso-cel in the next line of therapy if they start to progress well on pirtobrutinib.

Let's transition now to talk briefly about mantle cell lymphoma, including some recent data and a case. This case is a 55-year-old woman who presents with advanced-stage, stage IVB mantle cell lymphoma with some thrombocytopenia and splenomegaly. She has some other medical comorbidities as you see listed here. She undergoes frontline treatment with an aggressive chemoimmunotherapy regimen, hyper-CVAD with rituximab, and achieves a complete response. She gets consolidated with an auto transplant and, as is typical, relapses about 5 years later. So, the patient's now about age 60 and goes on ibrutinib. She does well for a couple of years but has now developed steady progression of the lymph node disease and they're now quite bulky. So, what are the treatment options for this patient? What would you recommend? Let's review some of the data now to help understand that.

First, let’s talk briefly about the OASIS study. This is an interesting study combining ibrutinib, venetoclax, and obinutuzumab in various arms. Also, an ibrutinib + obinutuzumab arm as well. It's a bit of a hodgepodge of a study because it includes both newly diagnosed mantle cell lymphoma patients as well as patients who have relapsed after auto transplant. And you can see the three arms here. The primary outcome here was safety because this was an early phase study, but there were secondary efficacy outcomes. Across the board across these three different cohorts, you saw high overall response rates in the 70% to 90% range or so, and they have

reasonable follow-up now at this point. Six-year PFS in the two relapsed cohorts was about 40% to 53%. And in that frontline cohort, it's an 80% 5-year PFS. This certainly does suggest that these different drugs when combined together in various ways can achieve high responses and also reasonable durability. So, these are all good things to consider. That being said, this type of ibrutinib-venetoclax-obinutuzumab triplet therapy is not an approved regimen for mantle cell lymphoma.

What about pirtobrutinib and relapsed/refractory mantle cell lymphoma? We do have data from the BRUIN study of mantle cell lymphoma with a median follow-up of about 8 months and you can see about 60% of patients had an ongoing response at that analysis. We recently saw some updated data from this study in the 90 patients pre-treated with a covalent BTK inhibitor, now with a median follow-up of about 12 months. Median duration of response was in the range of about 22 months. At the time of the analysis, close to a third of patients were ongoing in response, and the longest ongoing response was over 2 years. I think it's important to point out that the pirtobrutinib responses were also observed in patients post auto stem cell transplant and post CAR T-cell therapy.

What about pirtobrutinib in the real-world setting for mantle cell lymphoma? Relatively limited data here, but there is a compassionate use program that predated the approval of pirtobrutinib, and there were 10 patients who were tracked in that program. Very heavily pre-treated group of patients with relapsed mantle cell lymphoma with a median of three prior lines of therapy. But nonetheless, a 70% overall response rate, which is pretty similar, as you can see in the table, to what was observed in the BRUIN study. You can see that the 12-month duration of response was 71% outside of the clinical trial setting, and 12-month PFS was 56%. So, I think this does suggest that the promising results that were seen in the BRUIN study do apply outside of the clinical trial setting.

What about the real-world efficacy of subsequent lines of therapy, for example, CAR T-cell therapy? It is pretty common to see an initial response with CAR T-cell therapy, but it's that duration of response that's quite variable. There are now a number of different options that the NCCN guidelines list for this population. You can see that post-covalent BTK inhibitor, you can use a non-covalent inhibitor, you can use CAR T-cell–based therapy, you can use lenalidomide/rituximab. But from this French registry, a retrospective study with about 15 months of follow-up, you can see that post CAR T-cell the response rates are lower than what we're accustomed to seeing with these regimens pre CAR T-cell. With lenalidomide/rituximab, for example, only a 19% overall response rate, chemoimmunotherapy 23%. A little bit better when you get with the bispecific antibodies like a CD3xCD20 bispecific antibody, 43% overall response rate. You can see response with radiation, but that's often just for more localized progression events. This is an area where we need more data, but certainly the early data do suggest that in the post CAR T-cell setting the options are quite limited.

So, let's go back to our patient now and think about the available options. Remember, this is still a relatively young patient who is now 62 years old. She's been through intensive induction therapy for frontline treatment and then ibrutinib for about 2 years. We can think about what we'd recommend for this patient. I would say this is a patient where we're debating between CAR T-cell therapy or a non-covalent BTK inhibitor with pirtobrutinib. I think largely it's a similar discussion as what I would have with my CLL patients, in that often pirtobrutinib is the easier option logistically. It's likely to work for a period of time, and so most patients I think are choosing pirtobrutinib first but with the knowledge that that's not going to last forever and that they need to be thinking ahead to next steps and preparing for CAR T-cell therapy if they progress on pirtobrutinib.

It's certainly rewarding to see that we've made really excellent progress in the treatment of both relapsed/refractory CLL and mantle cell lymphoma. But of course these therapies aren't going to help patients if the patients can't get access to the therapies. So, Amy, you work with a lot of patients. Tell us a bit about some of the practical challenges that you have faced in helping your patients to access these novel therapies.

Amy L. Goodrich, RN, BSN, MSN, CRNP-AC:

Oh yes. They are real and they are many. If you look at these U.S. cancer disparities, we are all aware of disparities that exist in this country, unfortunately. Some of them are environmental. You can see here: air, water, transportation, housing, community safety. We have food deserts. We have communities where people have no green spaces. There are behavioral factors: tobacco use, smoking in general, diet, body weight, activity levels, adherence to screening and vaccinations. There are social factors: education level, income, employment, health literacy, the list goes on. There are clinical factors. Do you have access to health care? What is the quality of that health care? There are cultural factors and cultural health beliefs. There is a growing issue in this country with mental health issues and stress in general. And then the one thing that we can't change very readily are our biological and genetic factors. But this is really a multifactorial issue of disparity in this country.

What that means is barriers to cancer care. They may be insurance or financial. They may be that you have to drive 3 hours to your healthcare provider. You don't have healthcare providers in your immediate vicinity. You don't have access to screening or treatment. Do you have transportation? Are there cultural or language issues? We need robust education materials and programs to support people of all cultures and languages. And then we all know that patients do better if they have healthcare providers who look like them and speak the languages they do. And then educational and psychosocial support needs to be accessible to patients as well. So, again, multifactorial, very complex issues are barriers to cancer care.

Much of this is out of our control, but some of it that is within our control is shared decision-making. And, as Matt has done a great job outlining here, we have growing numbers of therapies and growing numbers of very good therapies, and there's no cookie cutter here. The shared decision-making is seeking the patient's participation and having them understand and explore and compare those treatment options, really assessing their preferences, reaching a decision with the patient, and evaluating with the patient is the key to optimizing adherence, drug adherence, and visit adherence, and improving outcomes in these patients. So, for example, starting a patient on a BTK inhibitor, most of us are in a multidisciplinary team. Hopefully all of us are working in a multidisciplinary team and we really do need consistent messaging to avoid confusion. Patient and caregiver counseling is part of getting a patient started on these therapies, and we're saying BTK inhibitor therapy, but this is any therapy and particularly these oral drugs that we are relying on patients to take and be adherent with at home. And then we need patient follow-up and continuity of care. This is getting to side effects early and getting them managed before they are significant.

So, segueing into continuity of care. Continuity of care is the extent to which healthcare services are received and coordinated. This is really looking at patient outcomes based on resource utilization. This group looked at Optum's healthcare claims database using this Herfindahl-Hirschman Index (HHI), which is a tool used for quality control in real-world data sets, and then of course the Continuity of Care Scale (CoCS). This group looked at just under 5,000 patients with CLL and 77.5% of them received a first-line covalent BTK inhibitor.

When we looked at scores—and the score range, for those of you who are not familiar with these scores, is zero to 1.0—the bottom line was with every 0.1 unit increase in the CoCS, so resource utilization and looking at

patient outcomes and their resource utilization. For patients who had better continuity of care, their odds of an emergency room (ER) visit were lower and their total ER visits were lower. The same was true for inpatient hospitalizations. The odds were lower, the numbers were lower, and there was a lower hazard of death. So, clearly good patient adherence and good follow-up are making a difference in their healthcare utilization outside of our clinics.

This leads us to this team-based approach and why this is so important with the patient and the caregivers in the middle, and all of us and all of our colleagues in our practices and our colleagues and different specialists, our medical oncologists, radiation oncologists, hematologists, nurses, nurse practitioners, physician associates, pharmacists, social workers. It may be nutritionists. We may need our gastroenterology folks to help us. This is really critical for managing these patients. And so, Matt, do you want to take us into our summary?

Matthew S. Davids, MD, MMSc:

Sure. Thanks, Amy. Great summary there. Just to wrap up, I think we're almost out of time here. I'm going to just give a brief summary of what we've discussed today. First, BTK inhibitors clearly are now being widely used across multiple hematologic malignancies, as you saw here with CLL and MCL. We have robust data sets now that we know that covalent BTK inhibitors are generally safe and effective drugs and that non-covalent BTK inhibitors can overcome resistance to the covalent BTK inhibitors. To some degree, all of these BTK inhibitors do have somewhat similar expected side-effect profiles. There are clearly some class effects here, but there is variation between these different BTK inhibitors in terms of the frequency and severity of those side effects. With all of these different options, shared decision-making really is needed now and comprehensive and ongoing patient education as well as diligent monitoring are critical to optimize patient outcomes.

Lastly, we'd like to leave you with some SMART goals, which are smart, measurable, attainable, relevant, and timely, and are intended to be actions that you can take back to your clinical practice starting today or tomorrow. So, the three SMART goals that we want to review are: First, to incorporate the latest clinical trial data regarding next-generation non-covalent BTK inhibitors into the care of patients with CLL, SLL, and mantle cell lymphoma as documented by treatment selection inpatient electronic health record (EHR) charts. Second, to improve management of potential AEs from treatment and provide clear patient education on steps that may mitigate AE severity. Third, to provide ideal patient care by involving the whole patient care team. Document shared decision-making, patient education, potential barriers to care, and guideline-concordant therapy administration in patient EHR charts.

To receive CME CE credit for today's program, complete the post-test and evaluation. You'll be able to download and print your certificate immediately upon completion. Again, thank you for joining us both today, and thank you for providing the very best care for your patients with CLL and MCL.

