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SOHO 2026 Debrief: Translating the Latest CLL Data Into Community Practice Decisions

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Dr. Brown:
Hello and welcome. I'm Dr. Jennifer Brown. Today I will be reviewing and summarizing key points in CLL from a symposium at the 2026 SOHO meeting.

Now, as you know, patients with first-line CLL can now choose between continuous and fixed-duration therapy. The continuous therapies are covalent BTK inhibitors, with or without an anti-CD20 antibody, and the approved drugs in that category are ibrutinib, acalabrutinib, and zanubrutinib.

Fixed-duration therapies are typically based on a BCL2 inhibitor, which currently is venetoclax, and that can be given in combination with an anti-CD20 antibody, obinutuzumab, covalent BTK inhibitor acalabrutinib or ibrutinib, or a covalent BTK inhibitor and anti-CD20, acalabrutinib and obinutuzumab.

So we now tend to focus on the second-generation BTK inhibitors in the frontline setting. So that includes acalabrutinib, which was approved based on the ELEVATE-TN study. This study compared acalabrutinib to acalabrutinib-obinutuzumab to obinutuzumab-chlorambucil and found that the median PFS was significantly higher, actually for acalabrutinib-obinutuzumab compared to acalabrutinib, and both of those were significantly higher than the obinutuzumab-chlorambucil. But this 16% improvement in 6-year progression-free survival with the addition of obinutuzumab was quite striking, and I think is a good reason to consider giving obinutuzumab if you are choosing a continuous acalabrutinib regimen.

The other second-generation BTK inhibitor that is currently in widespread use is zanubrutinib, and this was approved based on the SEQUOIA study, for which we now have 5-year follow-up. The main component of that study compared zanubrutinib to bendamustine-rituximab, and the estimated 5-year progression-free survival with zanubrutinib was 76% in that study. There's also a cohort for patients with deletion 17p who had a 66% 6-year progression-free survival, which was also quite good.

In the SEQUOIA study, also, there was an interesting arm combining zanubrutinib with venetoclax, and this was nominally an MRD-guided regimen, but in practice most patients continued the zanubrutinib because the criteria for stopping it were very, very stringent. So they more or less got continuous zanubrutinib with 2 years of venetoclax, and interestingly, this regimen actually equalized the outcomes in patients with deletion 17p or p53 and unmutated IGHV compared to those without. And this is somewhat unique in fixed-duration regimens, but of course, this was not truly fixed duration; it was MRD-guided, and many patients continued on zanubrutinib.

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Now, what about the venetoclax-based regimens? So CLL14 and CLL13 established fixed-duration venetoclax obinutuzumab as an effective frontline therapy, with 12 months of therapy, leading to a median progression-free survival overall of 6.4 years. And recently in the very long-term follow-up, the progression-free survival for low-risk patients is actually 9 years.

So which regimen do we choose? Well, the CLL17 study, which just came out this past year, addressed this by comparing continuous ibrutinib to fixed-duration venetoclax-obinutuzumab or fixed-duration venetoclax-ibrutinib. Now, the venetoclax-ibrutinib regimen is approved in Europe, not approved in the United States, although could be used. But in the US we've tended to favor using second-generation covalent BTK inhibitors. So with 3-year follow-up, which is admittedly too short, the progression-free survival comparing these 3 arms was identical. There were more progressions on the single-agent ibrutinib arm, but more deaths on the venetoclax-obinutuzumab arm.

And interestingly, we tend to think of continuous therapy being easier for older patients, but in this study, the continuous ibrutinib actually was worse in the unfit patients compared to the time-limited ven-obin or ibrutinib-ven, likely because the toxicity of ibrutinib is significantly greater than second-generation BTKs and does accumulate over time.

Now, we've recently seen the approval of acalabrutinib and venetoclax, and that was based on the AMPLIFY study, where acalabrutinib-venetoclax, with or without obinutuzumab, was compared to chemoimmunotherapy, and the 3-year progression-free survival for AVO was 83%, for AV was 76%, and for the chemoimmunotherapy was 66.5%. So the AVO was more effective in progression-free survival, but in overall survival, AV was actually better, and this was because there was an excess of deaths due to COVID in the AVO arm. If we censor for the COVID deaths, then the AVO does as well as the AV on overall survival. I think it's important to recognize that this study was done in the absolute height of the COVID pandemic around the world, where supportive care was variable, and prior to the availability of vaccinations. I think that the 3-drug regimen can be given safely to selected young, fit patients in our current environment.

So individual patient needs and preferences are key factors influencing our choice of first-line therapy. The continuous therapy has the advantage that it's very easy. Patient wants to spend 3/4 of the year in a state where you aren't; it's very easy to take care of them anyway. It's also effective in poor-risk subgroups. But the downsides are there's continuous treatment. There's the potential to generate resistance mutations. Adverse events tend to accumulate over time, even minor ones become intolerable if you're on the drug forever, and there's limited data in patients who stop therapy for adverse events. Although in my experience, if they've been on drug for some time, they can often do well.

Fixed-duration therapy minimizes the exposure period for toxicity, allows for treatment-free intervals, is particularly effective in IGHV-mutated CLL patients who can have very long durations of benefit. This potentially allows you to reuse the drugs in the future as well. The cons are mostly that the initial treatment takes a lot more work for the patient coming to clinic, and toxicity issues can be a little bit worse in that early period, but then that's equalized after patients go off the drug. And then we do know that there is a higher relapse risk in poorer genetic subgroups after fixed-duration therapy.

So the decision-making here includes CLL-specific factors, which we'll talk about a little more in a minute; patient factors like age, frailty, and organ function; and medication factors like the profile of adverse events, what other comorbidities the patient has, interactions, and availability.

So what about prognostic and predictive factors? So the really key ones in CLL are the IGHV mutation status, which you can test once at the beginning and it never changes, or you can test it at any time in the course of the disease and it will have been the same throughout the disease, or p53 alteration, which needs to be checked by both FISH for 17p deletion and by NGS for p53 mutation. And that can change, so that needs to be checked initially and then with each serial therapy.

And so we've known for a while that continuous BTK inhibitors, to some extent, equalize the worse outcome of unmutated IGHV while the patients are on the drug, and that's true for ibrutinib and acalabrutinib. For 17p deletion, we see that there is probably some drop-off even with continuous BTK inhibitors. And for example, in the SEQUOIA study, the 6-year PFS for patients without 17p was 74%, for those with was 64%. So not bad, but probably not quite the same. And in the ELEVATE-TN study, the patients on acala-obin had very similar outcomes regardless of IGHV status, but the 17p-deleted patients still did a little bit worse, more similar to the acalabrutinib patients.

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If we look at the venetoclax-based therapies, certainly in CLL14, the outcomes were worse for patients with p53 deletion or mutation with a median PFS of about 4 years, and those with unmutated IGHV have a median PFS of about 5.5 years. So still reasonably good, but less than you would get with a continuous BTK. But remember, you can repeat the venetoclax-obinutuzumab. And with venetoclax-obinutuzumab and other time-limited therapies, deeper remissions, as measured by undetectable MRD, are associated with longer progression-free survival, and this is usually measured at a 10^{-4} level.

In AMPLIFY with AV and AVO, we similarly see that unmutated IGHV patients do tend to drop off more quickly in their progression-free survival on the AV arm. But adding the obinutuzumab actually substantially equalizes this at 3 years, at least with the mutated IGHV patients, and the mutated IGHV patients did very well on all 3 arms.

Now, we know again from CLL17 that progression-free survival is similar at 3 years with all of these regimens. It's likely that will start to change when we get 5-year follow-up. So the 5-year follow-up is eagerly awaited. But another thing that we learned from CLL17 is that MRD is not necessarily comparable across the different regimens. So continuous ibrutinib had no undetectable MRD, which is entirely expected, and it doesn't matter if you stay on the ibrutinib. Ibrutinib-venetoclax rates of undetectable MRD were 40% to 47%, and venetoclax-obinutuzumab rates of undetectable MRD were 62% to 73%. Yet the PFS at 3 years was the same. So when we look at MRD, we know patients who achieve it do better within their given regimen compared to those who don't, but you can't necessarily compare it across regimens.

A number of studies have investigated MRD-guided regimens, where the duration of therapy is determined by the time it takes to achieve MRD. And so the best example of this is a study called FLAIR from the UK, where they actually measure when undetectable MRD occurs and then treat for twice that duration of time. So if you first reach undetectable MRD at 18 months, you get treated for 36 months. And with this regimen using ibrutinib plus venetoclax, they show a marked improvement in progression-free survival and even overall survival compared to continuous ibrutinib. And this is the only study that has shown that improvement in overall survival compared to a continuous BTK.

Now, the duration of therapy with the ibrutinib-venetoclax is longer than we see in CLL17. The median was about 27 months, and there are some patients who remain on therapy even longer. And so probably we need some adjustment of this regimen and some simplification of how it was done, but I think this does point us to perhaps a way that we can use time-limited therapy very effectively, even in our higher-risk patients in the future.

So in summary, what does all this mean for your practice? Well, the higher-risk unmutated patients or those with p53 alteration will have a shorter PFS with fixed-duration therapy like ven-obin or acala-ven. And particularly with the p53 alteration, most of us tend to favor continuous BTK treatment or an MRD-guided time-limited therapy. For unmutated IGHV, they can still potentially get ven-obin and do well, but one recognizes that their duration of remission will be shorter than those with mutated IGHV. Undetectable MRD correlates with longer PFS and fixed-duration therapy within these IGHV categories for VO and AV, but we don't want to compare them between regimens. An MRD-directed limited-duration therapy may mitigate the impact of high-risk features on long-term outcome.

So what about second-line therapy? So continuous BTK inhibitors are an option for second-line therapy in patients who haven't had them. In this setting, acalabrutinib has been directly compared to ibrutinib and found to be noninferior for progression-free survival and better tolerated across a wide range of side effects. Zanubrutinib has been directly compared to ibrutinib and found to be superior for progression-free survival and also better tolerated, particularly again reduced cardiac side effects. Hypertension was similar with zanubrutinib versus ibrutinib, but the time to event was reduced with zanubrutinib, and the degree of worsening was reduced with zanubrutinib compared to ibrutinib.

If a patient's been on a covalent BTK inhibitor, how do you figure out what treatment to use for them next? Well, if they stop the covalent BTK inhibitor for intolerance, you can potentially switch to a different covalent inhibitor. If someone's been intolerant to ibrutinib, you can try acala or zanu. If someone's been intolerant to acalabrutinib, you can try zanu. If a patient doesn't tolerate any covalent BTK, you can try pirtobrutinib, which we'll talk about in a minute. If the toxicity is severe enough, such as major bleeding, intracranial hemorrhage, ventricular arrhythmias, you can switch to BCL2 inhibitor-based therapy.

Now, on the other hand, if a patient discontinues a covalent BTK inhibitor for disease progression, then your options are BCL2 inhibitor-based therapy or pirtobrutinib.

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So in the second-line setting, venetoclax-rituximab was established as a regimen by the MURANO study. And in this study, the median PFS was 54 months, but these patients had not had any prior targeted therapy.

We've recently had data from the BRUIN CLL-322 study, which looked at pirtobrutinib with venetoclax-rituximab compared to venetoclax-rituximab in patients with relapsed refractory CLL. This study is important both for establishing the pirtobrutinib-venetoclax-rituximab regimen, and also because it actually shows us how venetoclax-rituximab behaves in the setting of prior covalent BTK inhibitors. Because most of the patients on this study had a prior covalent BTK inhibitor.

For those who discontinued their prior covalent BTK inhibitor due to progression, their median PFS was about 33 months. This is pretty consistent with what we saw in the prospective study in this setting by Jones et al., which was about 2 years.

The PVR study otherwise met its primary endpoint with a median follow-up of 27 months. PVR was superior for IRC-assessed progression-free survival compared to VR. The 2-year progression-free survival was 87% versus 72% with VR. But if we break this down based on prior BTK inhibitor treatment, we see that in those who had a prior covalent BTK, the benefit is very similar. Those who discontinued their prior covalent BTK due to progression had a better benefit, and those who had one prior covalent BTK inhibitor and discontinued according to progression had the best benefit.

So this regimen, which is not yet FDA-approved or in the NCCN Guidelines, but those things are likely coming, is most effective in our patients who've had progression on a prior covalent BTK inhibitor. Now, patients who'd had prior venetoclax were excluded from this study, and so that's a case where we wouldn't necessarily prioritize this study for those patients, but it could still be an option in that setting.

Now, your other option in your patient who's progressed with non-covalent BTK inhibitor would be to consider just a non-covalent BTK inhibitor on its own, and for that we have pirtobrutinib, which is approved, and nemtabrutinib, which is in clinical trials. They're very different drugs. Pirtobrutinib is very specific for BTK and has a similar IC50 against the C481S mutation, which is the most common resistance mutation, as it does against wild-type BTK. Nemtabrutinib is much less specific, inhibits many Src family kinases as well as MEK, and so there's even in vitro data suggesting that patients who have disease progression on pirtobrutinib or have resistance mutations to pirtobrutinib can still respond to nemtabrutinib.

And so the registration trial for pirtobrutinib in this setting was the CLL-321 study, which was a randomized comparison of pirtobrutinib monotherapy to investigator's choice of idelalisib-rituximab or bendamustine-rituximab. These patients were very high risk, with a median of 3 prior lines of systemic therapy, half with 17p deletion, almost 100% with unmutated IGHV, and 60% to 70% with complex karyotype. And in this study, pirtobrutinib improved progression-free survival compared to idelalisib-rituximab or BR, with a median PFS of 14 months versus 9 months.

Time to next treatment was also evaluated in this study and based on whether patients had had prior venetoclax or not, which was about half the population had had prior venetoclax. And so interestingly, those who were venetoclax naive had about a 30-month time to next treatment, while those who were venetoclax treated had about a 20-month time to next treatment. Now, whether this is just due to an extra line of therapy or specific to prior venetoclax exposure is not entirely clear.

We don't really know what the optimal sequencing is after a covalent BTK inhibitor. It may be that switching to a venetoclax-based regimen will help reset some of the resistance that we see to covalent BTK followed by pirtobrutinib, that would then make it easier to go back to pirtobrutinib. But at the moment, we don't know this. We have more data probably using venetoclax-based regimens after covalent BTK than we do pirtobrutinib-based regimens, and it's likely we'll get much more data on this in the future.

And nemtabrutinib is not yet approved. It's been studied in a phase 1 study in the BELLWAVE study, where it did have a progression-free survival of about 26 months in CLL-SLL patients, although this was reduced in those who were dual-class refractory to prior BTK and BCL2 inhibitor.

There are several ongoing potential registration trials for nemtabrutinib, and there was a report regarding resistance mutations, which found that in general C481S mutations tended to go down with nemtabrutinib, which is similar to what we see with pirtobrutinib, and it's also being studied in combination with venetoclax.

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So in summary, patients who have been treated with a covalent BTK inhibitor who have disease progression, you have options of a BCL2 inhibitor-based regimen or pirtobrutinib, and probably we'll have the pirtobrutinib-venetoclax-rituximab regimen in the near future as well. We don't really know yet which is best, but they can be used in either order.

Now, what's the next wave of coming treatment? So we have another category of BTK inhibitors coming, the BTK degraders. There are 2 of these that are advanced in clinical trials in phase 3 clinical trials, in fact. One called NX-5948, and one called BGB-16673. Both of these have been studied in heavily pretreated patients who are refractory to covalent BTK and venetoclax, and in general, many of them have also had pirtobrutinib. And despite this, the response rates are in the 80% to 85% range, and the progression-free survival that's been seen so far is in about the 2-year range. So these drugs are being combined, and they're also in registration trials where each company is actually comparing its degrader to pirtobrutinib head-to-head, which those are very interesting studies that we will look forward to the outcomes of.

And then, in terms of next-generation BCL2 inhibitors, there is sonrotoclax, which has in vitro more potent than venetoclax, and also has activity against the most common resistance mutation seen with venetoclax. This has been studied primarily in a combination with zanubrutinib, where it has been very highly effective in inducing high rates of undetectable MRD and prolonged progression-free survival, albeit still with relatively limited follow-up relative to the duration of treatment. The zanubrutinib-sonrotoclax combination has completed a registration trial, and we're just awaiting data for that.

The patients on continuous BTK inhibitors can develop a range of side effects, which are most prominent with ibrutinib usually, but can also be seen with acalabrutinib or zanubrutinib. This study shows data from patients who went on to receive acalabrutinib after being intolerant of ibrutinib, and the interesting take-home message from these intolerance studies is that patients come off for a wide variety of factors, and there's no one specific thing. Cytopenias can often be a problem. Bleeding, rash, arthralgia is a big problem with ibrutinib. Diarrhea also with ibrutinib. With acalabrutinib, patients can get headaches right when you start, but those almost always go away. I would say that arthralgia can actually be a problem with acalabrutinib, as can be bleeding or cytopenias, and that's similar with zanubrutinib, bleeding in particular with zanubrutinib. And so in the studies that have been done, typically many of the side effects do not recur if you change from ibrutinib to acalabrutinib or ibrutinib to zanubrutinib, but some will recur, but usually at about the same level. Generally, they don't get worse with the second-generation inhibitor compared to the first-generation inhibitor.

But when you have the patient who's kind of tired of their covalent continuous inhibitor and has some side effect, especially if it's something like atrial fibrillation or something that's medically significant, I like to give them a break off treatment if they've been on the drug for a number of years and are in a good remission. Typically, you can actually watch these people for quite some time. The data have suggested, for example, from ECOG 1912, if you are on the drug for 15 months, you could actually get a median of 2 years observation before you needed to start another therapy. So my personal practice is actually usually to just stop the covalent inhibitor if they've been on for a few years and have a side effect that's bothering them, and then reevaluate at the time of disease progression, starting over again. And this has the advantage that they probably have not become resistant to the covalent inhibitor, and so you can potentially use a different one again later.

Now that being said, some patients are very attached to their covalent inhibitor, or they may have very high-risk disease that you think really needs to stay on treatment, or their side effect may happen very early when they haven't had a deep response yet, and all of those would be reasons to try switching rather than taking a break. And for most of these side effects, like the arthralgias, cytopenias, it's perfectly fine to try a different covalent inhibitor. But if someone's had a major brain hemorrhage or ventricular arrhythmia, one of the very serious side effects that you can't really mitigate risk for, then I would probably switch to a venetoclax-based regimen at that point.

Now, the alternative situation, which is actually about equally common, is that patients develop progression while they're taking a continuous BTK inhibitor. And this can often be gradual, like the white count will start to creep up, or the lymph nodes will start to very slowly grow back. And the reason this can be gradual is because the patients often have developed a resistance mutation, but it's only at a low level, so it's not affecting most of the cells yet.

We know that the most common resistance mutation after covalent BTK inhibitor in failure is a C481S mutation, and that changes the covalent binding to non-covalent in the case of ibrutinib, or blocks binding entirely in the case of zanu and acala. We also know that zanu and acala have other mutations that show up also. So the L528W mutation occurs more commonly with zanu, and the T474I mutation more commonly with acala. Both of those mutations, though, are less frequent and often accompanied by C481S mutations that are more predominant with ibrutinib.

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Now pirtobrutinib, the non-covalent BTK inhibitor that's approved, will work against the C481S mutation that's most common, but the L528W and T474I mutations are resistance mutations for pirtobrutinib as well. That being said, we don't recommend that you screen or exclude people from getting pirtobrutinib based on these mutations, because the studies of pirtobrutinib have enrolled all-comers after BTK failure, and they have very high response rates. So it's quite reasonable to just treat a person who's had a prior covalent BTK with progression with pirtobrutinib without worrying about the resistance mutation profile.

And then after pirtobrutinib, there's another class in clinical trials called the BTK degraders. So we may soon have 3 lines of BTK inhibitor–targeting therapy for our CLL patients.

For time-limited venetoclax-based therapy, the primary complication that we worry about is tumor lysis syndrome, and this can happen because the drug kills the CLL cells so quickly that the electrolytes can become markedly abnormal. And in the phase 1 studies of venetoclax, this even led to a few deaths. And so as a result, we have a very strict monitoring protocol for how we escalate venetoclax toward its recommended dose.

However, as we have been using venetoclax more, we're learning that this intensive monitoring may not be as necessary as it seems. There are 2 independent real-world cohorts, one from the Fred Hutch and one from the Levine Cancer Institute, that found that clinical TLS was essentially absent, and laboratory TLS was quite rare, even with somewhat imperfect monitoring adherence. So this does support a less intensive TLS monitoring schedule.

I think if we think about this, though, it's very important to think about who your patient is. So a patient who has started on a covalent BTK inhibitor, for example, acalabrutinib and is starting venetoclax 2 or 3 months later is very low risk usually because their disease has been cytoreduced, although some of them may still have an elevated white count, and then that needs to be taken account of as not as low risk as someone who has normalized their white count and their lymph nodes.

In contrast, especially in the early days of venetoclax, we were often initiating the drug in patients who had very aggressive progressions after covalent BTK inhibitor with a very large disease burden, and so that was some of the setting in which the severe tumor lysis was seen, and so those patients are very high risk, and those are the ones that needed to be treated as high risk then and now, whereas some of these patients who have had a lead-in with other therapies and cytoreduction are much lower risk.

And there is an ongoing study called VENETIAN, which is optimizing the venetoclax ramp-up and TLS risk with the type of lead-in that we're now using, particularly in frontline CLL.

There are other studies that have explored accelerated venetoclax ramp-up daily inpatient, which is again another option if you have a patient who has a high disease burden and needs to get on drug quickly to do this safely, or alternatively, just for convenience, so that they don't have to come into clinic for 5 weeks.

There is also an escalated inpatient ramp-up being explored for the novel BCL2 inhibitor sonrotoclax.

So in terms of venetoclax ramp-up monitoring, there are ongoing efforts to prospectively study the safety of modifying this ramp-up and its monitoring requirements. However, until there are changes to the approved venetoclax label, the ramp-up schedule and associated monitoring should still be performed according to the currently approved prescribing information. And team-based adherence monitoring and patient education is very useful for oral targeted therapy.

One of the final practice-related issues that comes up when using any of these drugs is that there are important drug interactions that occur, particularly with CYP3A4 moderate and strong inhibitors. So antifungal agents, for example, interact significantly with all of our BTK inhibitors and venetoclax, and it's particularly a problem during the venetoclax ramp-up. So this is something to be sure to check with your pharmacist and think about as you are considering prescribing these drugs.

And then patients on BTK inhibitors, we generally need to hold the drug 3 days before and after a minor surgical procedure, and 7 days before and after a major surgical procedure, in order to avoid bleeding. And because of the bleeding risk, also, we usually don't use, for example, dual antiplatelet therapy together with a BTK inhibitor, which would end up being triple antiplatelet therapy, but we do have good experience with a BTK inhibitor plus aspirin or BTK inhibitor plus apixaban when needed, but we try to avoid all 3.

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So in terms of take-home messages from the SOHO meeting, we now have another time-limited therapy option, an all-oral regimen of acalabrutinib-venetoclax, in addition to venetoclax-obinutuzumab. And I think most of us favor the use of these time-limited regimens for our patients as compared to continuous BTK, especially in the lower-risk patients. So AV was just approved by the FDA in February, and so that is a relatively new option to explore for your patients.

And then, for patients who've had progression on a covalent inhibitor, there are the options of a venetoclax-based regimen, venetoclax with anti-CD20 usually, or pirtobrutinib, and soon there'll be the option of pirtobrutinib-venetoclax-rituximab, which was reported at EHA and published at the same time and will soon also be in clinical use. And that is probably most important for patients who have had progression on a prior covalent BTK inhibitor.

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