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The First Approved All-Oral, Fixed Duration Treatment for CLL: Insights from the AMPLIFY Trial

Announcer:
You're listening to *Project Oncology* on ReachMD.

This program, titled "The First Approved All-Oral, Fixed Duration Treatment for CLL: Insights from the AMPLIFY Trial," is sponsored by AbbVie Oncology US Medical Affairs.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Welcome to *Project Oncology* on ReachMD. I'm your host Dr. Jennifer Caudle, and today, we'll be discussing data from the Phase 3 AMPLIFY clinical trial. This trial evaluated the efficacy and safety of all-oral, fixed-duration regimen of venetoclax/acalabrutinib versus chemoimmunotherapy in patients with previously untreated chronic lymphocytic leukemia—or CLL for short—without 17p deletion or *TP53* mutation.[1]

Joining me today to explore these data and what they mean for first-line treatment decisions in CLL is Dr. Nicole Lamanna.

Dr. Lamanna is the Judy Horrigan Professor of Medicine and Director of the CLL Program in the Hematologic Malignancies Section of the Hematology/Oncology Division at Columbia University Irving Medical Center in New York.

Dr. Lamanna, we're so glad to have you here today.

Dr. Lamanna:
Thank you, I'm happy to be here.

Dr. Caudle:
Now before we dive in, let's review the approved indication for venetoclax tablets.

Announcer:

Indication

- **Venetoclax is a BCL-2 inhibitor indicated for the treatment of adult patients with CLL or SLL.**

Dr. Caudle:
With that in mind, let's get started. When we think about first-line CLL management, we've seen the treatment landscape evolve quite a bit, with targeted therapies and fixed-duration approaches entering the conversation.[2] Given that context, Dr. Lamanna, how does venetoclax/acalabrutinib add to the CLL treatment landscape?

Dr. Lamanna:
That's a really great question, and I think it really speaks to where we are in CLL management right now. Targeted therapies allow us to offer patients a continuous or a fixed-duration treatment approach.[2] In the case of venetoclax/acalabrutinib, we now have the first approved, all-oral, fixed-duration treatment option that doesn't require oncolytic infusions.[1]

This is important because, alongside efficacy and safety, other factors—such as administration and duration of therapy—may also play a role in discussing treatment options with their doctor for patients. So when discussing frontline options, we should align our approach

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with each patient's disease characteristics and goals of care.[3-5]

Dr. Caudle:
And that leads us right into the Phase 3 AMPLIFY trial. We'll talk about the results in a moment, but before we do, could you give us a brief overview of the study design and patient population?

Dr. Lamanna:
Yeah, absolutely. AMPLIFY was a randomized, multi-center, open-label Phase 3 study that evaluated the combination of venetoclax plus acalabrutinib—the first all-oral, fixed-duration regimen—versus the investigator's choice of chemoimmunotherapy, also known as CIT. The CIT control arm included either fludarabine-cyclophosphamide-rituximab, known as FCR, or bendamustine-rituximab, known as BR. Patients included in the trial had previously untreated CLL and did not have a 17p deletion or a *TP53* mutation.[1]

Patients were stratified by age, IGHV mutational status, Rai stage, and geographic region, and were randomized in a one-to-one fashion with an additional investigational treatment arm.[1]

In terms of dosing, venetoclax plus acalabrutinib was administered for 14 cycles. Patients started with acalabrutinib 100 milligrams orally approximately every 12 hours for two cycles, and then venetoclax was initiated at Cycle Three, Day One with a four-week ramp-up to 400 milligrams, starting week five. The entire regimen was completed after 14 cycles of 28 days each.[1]

The primary endpoint of AMPLIFY was progression-free survival, or PFS, assessed by an independent review committee. Key secondary endpoints included undetectable minimal residual disease, or uMRD, in the peripheral blood, overall survival, response rates, and time to next treatment.[1,2]

Dr. Caudle:
Speaking of, let's get into those primary results. You know, what were the trial findings for PFS?

Dr. Lamanna:
So the trial met its primary endpoint, demonstrating a 35 percent reduction in the risk of progression or death in the venetoclax/acalabrutinib treatment arm compared to the CIT arm.[1]

The median PFS wasn't reached with venetoclax/acalabrutinib at a median follow-up of 42.6 months. In the FCR/BR arm, the median PFS was 47.6 months.[1]

Now, let's turn to PFS data by IGHV status. Keep in mind that this exploratory analysis of PFS subgroups wasn't powered or tested for statistical significance. Additionally, small patient numbers and differences in subgroup demographics and disease characteristics limit our ability to interpret this data.

However, in patients with mutated IGHV, the 36-month PFS in the venetoclax/acalabrutinib arm, which was assessed about two years off treatment, was 86.0 percent. In the CIT arm, it was 79.9 percent.[2]

And in patients with unmutated IGHV, the median PFS was 51.5 months with the venetoclax/acalabrutinib combination—representing over three years off treatment—compared to 43.3 months with CIT.[2]

Dr. Caudle:
Thanks for walking us through those findings. Now, the trial also evaluated overall survival, response rates, and uMRD. Looking at the data, how do you interpret these secondary endpoints?

Dr. Lamanna:
So let's start with overall survival. With about two years off treatment at a median follow up of 41 months, the overall survival rate for the venetoclax/acalabrutinib patients was 94.1 percent, versus 85.9 percent in the CIT group.[2]

And then looking at the response rate, patients receiving venetoclax/acalabrutinib had a higher percent—with an overall response at 93 percent, versus 75 percent of patients in the CIT group.[1]

Now, the uMRD data require some context, and I think it's helpful to discuss this transparently. In the intent-to-treat population, all randomized patients are included regardless of whether an MRD assessment was actually performed, and missing assessments are counted as MRD-positive.[2]

In this population, 26.8 percent of patients achieved uMRD at the key secondary endpoint, which, for the venetoclax/acalabrutinib arm, was at cycle nine when treatment was ongoing.[2]

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If we examine the evaluable population as an exploratory endpoint, we're looking at the patients who actually had an MRD assessment performed at the specified timepoint. In this population, 45 percent achieved uMRD at the end of treatment, and 38 percent had uMRD three months after the end of treatment in the venetoclax/acalabrutinib arm.[2]

It's also worth noting that if we look at the whole picture, we observe a 76.5 percent off-treatment PFS, 88.5 percent time to next treatment results, and a 93 percent overall response rate.[1,2]

While these exploratory endpoints provide additional context, they should also be interpreted alongside the primary endpoint of PFS.

Dr. Caudle:
For those of you who are just tuning in, you're listening to *Project Oncology* on ReachMD.

I'm your host Dr. Jennifer Caudle, and today, I'm speaking with Dr. Nicole Lamanna about what the Phase 3 AMPLIFY trial data mean for frontline CLL treatment decisions.

Dr. Caudle:
So, Dr. Lamanna, one endpoint that's been getting increasing attention as fixed-duration regimens become more familiar is time to next treatment, or TTNT.[6] That said, how do you think about TTNT in the context of AMPLIFY?

Dr. Lamanna:
TNT is particularly relevant for fixed-duration regimens because it captures something that goes beyond disease progression—it tells us how long patients actually remain off treatment after completing a defined course of therapy.[6] And that's often something that patients care about deeply.[3]

In AMPLIFY, 88.5 percent of patients treated with venetoclax/acalabrutinib didn't need to start another line of CLL treatment at approximately two years after completing therapy. In comparison, that figure was 75.2 percent in the CIT arm.[7,8]

So when I'm translating that into a conversation with a patient, I'll often say: "*This is a fixed-duration treatment, and many patients are able to complete therapy and remain off treatment for a period of time before needing a subsequent line of therapy.*"

Dr. Caudle:
That's a really practical way to frame it. And now, looking at the safety profile, what should clinicians expect when using this combination?

Dr. Lamanna:
That's a good question. The safety profile of venetoclax/acalabrutinib in AMPLIFY was consistent with the known safety profile of each agent individually.[1,2,9]

With venetoclax/acalabrutinib, treatment exposure was limited to 14 cycles of fixed-duration treatment. The most common adverse events—those of any Grade occurring in 20 percent or more of patients—were neutropenia, lymphopenia, any infection, thrombocytopenia, anemia, headache, diarrhea, musculoskeletal pain, and COVID-19.[1,2]

It's also helpful to look at selected adverse events of clinical interest. For example, while neutropenia does occur with venetoclax, the rate of febrile neutropenia in the trial was only 1.7 percent in the venetoclax/acalabrutinib arm compared to nine percent in the CIT arm.[1,2]

And because tumor lysis syndrome, or TLS, is a potential risk [SH20.1]with venetoclax initiation, the trial also evaluated TLS rates. No clinical TLS was observed in either study arm when venetoclax onboarding was conducted as per label.[1,9] Laboratory TLS occurred in one patient in the venetoclax/acalabrutinib arm compared with eight patients in the CIT arm.[2,9]

Another area to consider are cardiovascular and bleeding events associated with BTK-inhibitors, such as acalabrutinib. Any-Grade atrial fibrillation occurred in only 0.7 percent of patients, and any-Grade hypertension was only seen in four percent.[2]

Serious adverse events were reported in 25 percent of patients receiving venetoclax/acalabrutinib. The most common of these, at two percent or greater, included infections, COVID-19 and COVID-19 pneumonia, second primary malignancies, and neutropenia. And fatal adverse events occurred in 3.4 percent of patients, most commonly due to COVID-19 and COVID-19 pneumonia.[1]

Dose modifications, including reductions and interruptions, were part of the clinical trial protocol.[2] For venetoclax, dose modifications due to neutropenia included dose interruptions in 21 percent of patients, reductions in seven percent, and discontinuations in 0.3 percent.[1] The majority of patients who required dose adjustments were still able to continue and complete the regimen.[2,8,9]

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Dr. Caudle:
So, Dr. Lamanna, to bring all of this together, how might the results from AMPLIFY affect your conversations with patients about frontline treatment options for CLL?

Dr. Lamanna:
Well as we discussed, the data from AMPLIFY demonstrated the efficacy and well-characterized safety profile of this venetoclax/acalabrutinib combination in previously untreated CLL and supported the approval of a new label indication for this combination regimen.[1]

Patient preference is a key consideration in selecting the right fit for their treatment goals.[5] Venetoclax fixed-duration regimens offer the possibility of time-limited treatment and the chance to reduce cumulative drug exposure and its associated toxicities.[9,10] And now we have an additional fixed-duration treatment option in the frontline setting—one that is all-oral, which offers the flexibility to further individualize therapy.[1]

Dr. Caudle:
Those are helpful insights, Dr. Lamanna. Do you have any additional closing remarks or clinical perspective on the evolving CLL landscape?

Dr. Lamanna:
Ultimately, having multiple effective regimens in our frontline toolkit is a positive development as it expands the choices available to our patients. And I think that's very important, again.

Dr. Caudle:
Absolutely. And that's a great way to round out our discussion today. I'd like to thank my guest, Dr. Nicole Lamanna, for her insights into the AMPLIFY trial data and what they mean for frontline CLL treatment decision-making.

Before we close, let's take a moment to review some important safety information.

Announcer:

INDICATION

- Venetoclax is a BCL-2 inhibitor indicated for the treatment of adult patients with CLL or SLL.

DOSAGE AND ADMINISTRATION

- CLL/SLL 5-week dose ramp-up schedule: Administer venetoclax according to a weekly ramp-up schedule over 5 weeks to the recommended oral daily dose of 400 mg, as follows: 20 mg daily (Week 1), 50 mg daily (Week 2), 100 mg daily (Week 3), 200 mg daily (Week 4), 400 mg daily (Week 5 and beyond).
- Venetoclax + acalabrutinib: Start acalabrutinib 100 mg orally approximately every 12 hours until disease progression, unacceptable toxicity or completion of 14 cycles of treatment. Each cycle is 28 days. Refer to the acalabrutinib prescribing information for additional dosing information. Cycle 3 Day 1 (C3D1): start venetoclax according to the 5-week ramp-up dosing schedule. After completing the ramp-up phase, continue venetoclax at a dose of 400 mg orally once daily until disease progression, unacceptable toxicity, or until the last day of C14.
- Venetoclax + obinutuzumab: Start obinutuzumab administration at 100 mg on C1D1, followed by 900 mg on C1D2. Administer 1000 mg on C1D8 and C1D15 and on D1 of each subsequent 28-day cycle, for a total of 6 cycles. Start venetoclax on C1D22, according to the 5-week ramp-up dosing schedule. After completing the ramp-up phase on C2D28, continue venetoclax at a dose of 400 mg orally once daily from C3D1 until the last day of C12.
- Venetoclax + rituximab: Start rituximab administration after the patient has completed the 5-week ramp-up dosing schedule for venetoclax and has received the recommended dosage of 400 mg orally once daily for 7 days. Administer rituximab on D1 of each 28-day cycle for 6 cycles, at a dose of 375 mg/m^2 IV for C1 and 500 mg/m^2 IV for C2–C6. Continue venetoclax 400 mg orally once daily for 24 months from C1D1 of rituximab.
- Take venetoclax tablets orally once daily with a meal and water. Do not chew, crush, or break tablets.
- Provide appropriate prophylaxis for TLS.

Contraindication

- **Strong CYP3A Inhibitors:** Concomitant use with strong CYP3A inhibitors at initiation and during ramp-up phase in patients with

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CLL/SLL is contraindicated.

Warnings and Precautions

- **TLS:** TLS, including fatal events and renal failure requiring dialysis, has occurred in patients treated with venetoclax. Anticipate TLS; assess risk in all patients. Premedicate with anti-hyperuricemics and ensure adequate hydration. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases.
- **Neutropenia:** Monitor blood counts. Interrupt dosing and resume at same or reduced dose. Consider supportive care measures.
- **Infections:** Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with venetoclax. Monitor patients closely for signs and symptoms of infection and treat promptly. Withhold venetoclax for Grade 3 and 4 infection until resolution and resume at same or reduced dose.
- **Immunization:** Do not administer live attenuated vaccines prior to, during, or after venetoclax treatment until B-cell recovery.
- **Embryo-Fetal Toxicity:** May cause embryo-fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.
- **Increased mortality in patients with MM when venetoclax is added to bortezomib and dexamethasone:** In a randomized trial in patients with relapsed or refractory MM, the addition of venetoclax to bortezomib plus dexamethasone, a use for which venetoclax is not indicated, resulted in increased mortality. Treatment of patients with MM with venetoclax in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

Adverse Reactions

- In CLL/SLL, the most common adverse reactions (≥20%) for venetoclax when given in combination with obinutuzumab or rituximab or as monotherapy are neutropenia, thrombocytopenia, anemia, diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, fatigue, and edema. In CLL/SLL, the most common adverse reactions (≥20%) for venetoclax when given in combination with acalabrutinib are neutropenia, headache, diarrhea, musculoskeletal pain, and COVID-19.

Review full prescribing information at www.rxabbvie.com or contact AbbVie Medical Information at 1-800-633-9110 or go to abbviemedinfo.com.

Dr. Caudle:
And with that important safety information in mind, we've come to the end of our program.

Dr. Lamanna, it was great speaking with you today.

Dr. Lamanna:
Thanks, it's been a pleasure.

Announcer:
This program was sponsored by AbbVie Oncology US Medical Affairs. If you missed any part of this discussion or to find others in this series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge.

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