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What to Know About a Treatment Option That Targets BCL2

ReachMD Announcer: Welcome to ReachMD.

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Dr. Turck: The anti-apoptotic protein B-cell lymphoma 2, or BCL2 for short, is a key regulator of the intrinsic apoptotic pathway and is often overexpressed in chronic lymphocytic leukemia cells. For this reason, BCL2 represents an important therapeutic target for CLL, and today, we're going to be looking at a treatment option that targets this protein.

This is ReachMD, and I'm Dr. Charles Turck. Joining me is Dr. Nicole Lamanna, an associate clinical professor of medicine at Columbia University Medical Center. Dr. Lamanna, it's great to have you with us.

Dr. Lamanna: Thank you. It's great to be joining you.

Dr. Turck: So, Dr. Lamanna, let's get an overview of this targeted therapy for CLL, which is called venetoclax. Can you tell us about this treatment option to start?

Dr. Lamanna: Venetoclax is a BCL-2 inhibitor that is a potent, highly selective oral agent. BCL-2 is an anti-apoptotic protein that is overexpressed in CLL cells, so venetoclax helps to restore apoptosis in CLL patients, which is one indication it's been approved for.

Venetoclax demonstrates clinical effectiveness in CLL to induce rates of remission and undetectable MRD, even in patients who have adverse features such as 17p deletion.

Dr. Turck: And who, specifically is venetoclax indicated for, and what does the dosing schedule look like?

Dr. Lamanna: Venetoclax is indicated for patients with CLL or SLL, both in frontline and in the relapsed or refractory setting. In the frontline setting, it is approved in combination with obinutuzumab and that duration of treatment is twelve months. In the relapsed setting, it's approved in combination with rituximab, and it's given in 24 months in that circumstance. It's an oral agent, and there is a dose ramp-up that's done weekly over five weeks, starting at 20 mg, then 50 mg, 100 mg, 200 mg, with a recommended daily dose of 400 mg.

It is ramped up to monitor for tumor lysis syndrome and to allow patients to have repeat laboratory work so that we're able to ensure the safety of the patients as we look at their electrolytes and make sure that their kidney function is doing well.

Dr. Turck: So now that we have that important baseline established, I'd like to focus on the clinical trials that investigated this treatment option. Dr. Lamanna, what can you tell us about the studies looking at the efficacy and safety of venetoclax for CLL in first-line settings?

Dr. Lamanna: The study that led to its approval in the frontline setting was this randomized, multicenter Phase 3 trial, CLL14, in previously untreated CLL with co-existing medical conditions. This was a randomization of venetoclax-obinutuzumab versus obinutuzumab and chlorambucil. This study was designed to evaluate the efficacy and safety of this twelve-month fixed duration of

venetoclax and obinutuzumab versus six cycles of obinutuzumab and twelve cycles of chlorambucil.

The venetoclax/obinutuzumab combination showed a 67% reduction in the risk of progression or death versus the obinutuzumab-chlorambucil arm, and complete responses were seen in about 50% of patients, with a high level of undetectable, minimal residual disease in this patient population.

What we were seeing was that there was a nice depth of remission, including, in 57%, undetectable disease in the bone marrow, and 76% in the peripheral blood. In the study, the threshold for undetectable minimal residual disease was defined as <1 CLL cell per 10,000 leukocytes (or 10^{-4}).

In terms of progression-free survival, a post-hoc follow-up analysis showed 82% at 36 months for the venetoclax-obinutuzumab arm, compared to 50% for the obinutuzumab-chlorambucil arm. This really established quite a nice level of response for patients in frontline setting, with a fixed duration of treatment with venetoclax and obinutuzumab in comparison with a regimen with obinutuzumab and chlorambucil, which has traditionally been used for older, frailer patients with CLL.

Dr. Turck: And how about the relapsed/refractory setting? Have there been any trials evaluating Venetoclax in patients who received therapy before?

Dr. Lamanna: In the relapsed setting, in terms of looking at how this regimen compared with more traditional chemoimmunotherapy, there was a randomized study called MURANO with a control arm of bendamustine and rituximab. Prior to targeted agents being approved and used more widely than chemoimmunotherapy, bendamustine/rituximab was a very common relapsed/refractory regimen to give in this setting, and also to older, frailer persons in the frontline or relapsed setting. So, bendamustine/rituximab in relapsed was very commonly used, and this was a study that looked at venetoclax/rituximab versus bendamustine/rituximab .

When we talk about the notion of fixed duration therapy, this really initiated in the relapsed refractory setting, looking at rituximab given with a 24-month fixed duration of venetoclax therapy.

In this study, it showed that there was superiority of the venetoclax/rituximab in terms of progression-free survival; an 81% reduction in the risk of progression or death compared with the bendamustine/rituximab arm. The median PFS was not yet reached in the venetoclax/rituximab arm versus 18 months in the bendamustine/rituximab arm. There was a benefit in terms of 24-month rates of at 85% versus 38%, respectively.

CR/CRi rates were also higher in the venetoclax/rituximab arm compared with the bendamustine/rituximab arm, 8% versus 4%, although these differences in CR rates were not statistically significant.

A follow-up, post-hoc analysis at 5 years showed a median PFS of 53.6 months in the venetoclax/rituximab arm versus 17.0 months in the bendamustine/rituximab arm.

These data are currently under evaluation by the FDA.

Again the venetoclax/rituximab arm here as fixed duration of treatment compared with bendamustine/rituximab, which is also fixed duration, had a much more enhanced progression-free survival in venetoclax/rituximab versus bendamustine/rituximab. The rate of undetectable MRD in the peripheral blood for venetoclax/rituximab was 53% vs 12% in the bendamustine/rituximab arm. That really solidified venetoclax/rituximab in terms of its FDA approval, but this was really the first study taking an oral agent and saying, “Hey, can we look at a fixed duration because of the PFS benefit and depth of response achieved here.”

For both the MURANO study in the relapsed setting and the CLL14 study in the up-front setting, we’re following these data annually to look at both the long-term progression-free survival and overall survival as well as to gain knowledge about how to better utilize MRD in this setting.

Dr. Turck: That’s great, Dr. Lamanna. Now that we have an understanding of venetoclax’s efficacy, let’s talk about the safety results from these trials. What can you tell us about those?

Dr. Lamanna: With venetoclax, there are a couple of key things to look out for – how we use this agent and monitor for some of its potential adverse events is important. Tumor lysis syndrome, as noted earlier, is something we need to be vigilant for, especially based on the bulk of somebody’s disease burden, whether they have a high white blood cell count or bulky disease, we’re going to monitor more intensely for tumor lysis syndrome in the beginning, and also in cases where a patient has had an ongoing dose interruption and needs to resume therapy. Depending upon if the patient has some renal insufficiency or they’re high risk, for those patients often times require hospitalization. Monitoring their electrolytes, and administering extra hydration and medications to reduce their uric acid levels are similar to what we used to do with chemoimmunotherapy. That being said, by being prophylactic and aggressive, the amount of tumor lysis syndrome seen in the clinical trials is actually very low.

Now, what are the other common events that I explain to patients that we can often see with this drug? Given that this drug works so well on the bone marrow, it is not uncommon to have some myelosuppression with this agent. There are a fair number of patients who can become neutropenic or have some mild anemia as well.

In the MURANO trial, neutropenia was the most frequent adverse reaction, occurring in 65% of patients treated with venetoclax/rituximab. Neutropenia was also the most frequent adverse reaction in the CLL14 trial, occurring in 60% of patients treated with venetoclax/obinutuzumab.

The use of growth factors is something that I do routinely in clinical practice. If somebody has neutropenia that is persistent, despite growth factor use, sometimes one might need to dose reduce the agent, as well.

I'll often explain to patients that they might have some GI issues. They can have nausea or diarrhea, and most of these are usually transient in nature. In the MURANO trial, 40% and 21% of venetoclax/rituximab patients experienced any grade of diarrhea and nausea, respectively. Diarrhea and nausea were also observed in the CLL-14 trial in 28% and 19% of patients, respectively.

I often will prescribe antinausea medicines preemptively so they have it if they should get nauseous at home. An antidiarrheal agent is all that is needed typically. It is uncommon that I've had to pull somebody off of therapy due to GI issues.

Patients can experience fatigue, and certainly some of that might be tied into their disease; when their disease gets better, they feel better and their fatigue also gets better as well.

For all our CLL patients, we're always concerned about the risk of infection. In the MURANO trial, the most common grade 3 or higher infection that occurred in patients treated with venetoclax/rituximab was pneumonia, at 7%. In the CLL14 trial, 1% of patients experienced grade 3 or higher upper respiratory tract infections.

In my practice, many patients are hypogammaglobulinemic, and we're always concerned about respiratory tract infections, sinusitis, and skin infections. We can see an increased incidence of infections, particularly in our relapsed refractory patient population. If there is an infection, they need to notify us immediately so we can treat accordingly along with their therapy. If I think that an infection requires hospitalization or something more extreme, I may hold therapy temporarily, but typically, if it's something mild and they need to take some oral antibiotics but are otherwise doing well, oftentimes I'll just support them through it and keep a close eye on worsening of any infectious complications.

Dr. Turck: Dr. Lamanna, before we close out today's discussion, I'd like to hear from you regarding the take-home messages you think clinicians should come away with here.

Dr. Lamanna: I think that many of us would agree that for patients – and actually, for clinicians too – it's really been a wonderful time to be able to help patients with CLL because we have so many treatment options.

Given these remarkably active therapies we really now can actually start selecting treatment options based on some of the preferences of our patients. These agents really help folks that have low risk disease, or what we'd consider more favorable prognostic markers, but they also treat very well patients with undesirable or less favorable prognostic markers as well. We really have excellent therapy for patients who have the most aggressive or adverse features associated with this disease.

We're really quite fortunate in this time period to have multiple therapies and can often choose what may suit the needs of our patients, depending upon their comorbidities, whether chronic, indefinite therapy might be better for some patients, versus a fixed-duration therapy.

Despite how fearful many patients are as they first embark on their initial therapy because they've never done this before, for clinicians, it's really a wonderful time to support them. Clinicians should nurture that and be reassuring to patients that they have really excellent treatment options currently available.

Dr. Turck: Thanks, Dr. Lamanna. Now let's take a moment to review some important information for venetoclax.

ReachMD Announcer:
Indication:

- Venetoclax is a BCL-2 inhibitor indicated for the treatment of adult patients with chronic lymphocytic leukemia (or CLL) or small lymphocytic lymphoma (or SLL).

Contraindications:

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

CLL/SLL is contraindicated.

Warnings and Precautions

- **TLS:** Tumor lysis syndrome (or 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 (intravenous hydration, frequent monitoring, and 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 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 multiple myeloma (or 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 and SLL, the most common adverse reactions (≥20%) for venetoclax when given in combination with obinutuzumab or rituximab or as monotherapy were neutropenia, thrombocytopenia, anemia, diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, fatigue, and edema.

Review full prescribing information for additional information at www.rxabbvie.com or contact AbbVie Medical Information at 1-800-633-9110.

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