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Mapping CLL Treatment Endpoints: PFS and TTNT in Fixed vs Continuous Therapy

**Announcer:**
You're listening to *Project Oncology* on ReachMD. This medical industry feature, titled "Mapping CLL Treatment Endpoints: PFS and TTNT in Fixed vs Continuous Therapy," is sponsored by AbbVie US Medical Affairs. Here's your host, Dr. Charles Turck.

**Dr. Turck:**
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Today, we're diving into how we define and interpret key treatment endpoints in chronic lymphocytic leukemia, or CLL. We'll look at progression-free survival and time to next treatment in the settings of fixed-duration and continuous treatments.

Joining me to discuss these endpoints is Dr. Carter Davis, who's the Section Head of the Hematologic Malignancies and Cell Therapy Section at Ochsner MD Anderson Cancer Center in New Orleans, Louisiana. Great to have you here, Dr. Davis.

**Dr. Davis:**
Thanks, I'm happy to be here.

**Dr. Turck:**
Well let's start by reviewing some fundamental concepts. The 2018 Guidelines from the International Workshop on Chronic Lymphocytic Leukemia outlined key clinical measures for evaluating CLL treatments. Can you walk us through how they define progression-free survival and time to next treatment?

**Dr. Davis:**
Certainly. These measures are foundational endpoints that help ensure we're all speaking the same language — whether it's trials, research, or clinical care. To start, progression-free survival, or PFS, is the time from when a patient starts treatment to disease progression or death.[1] Time to next treatment, or TTNT, *also* begins when a patient starts treatment, but it ends when they start the next line of therapy or they pass away.[1]

PFS is often the primary endpoint in oncology clinical trials because it's a well-established measure of how effectively a therapy delays disease progression.

TTNT can be a valuable measure in practice because it provides a patient-centric point of view. Knowing how long a patient can go before needing additional therapy offers a meaningful lens when we're thinking about their real-world experience.

**Dr. Turck:**
So given that important context, let's turn to the current CLL treatment landscape. What are the main approaches, and how do they impact long-term treatment planning?

**Dr. Davis:**
Treatment selection in CLL generally follows one of two strategies: fixed-duration therapy or continuous therapy, which is also called treat-to-progression. Each has different implications for long-term management and patient experience.

Fixed-duration therapy involves treating for a set period of time prior to coming off treatment. We continue to monitor patients while off therapy, and we'll only start further treatment if disease progression occurs and clinical symptoms or characteristics justify it.

Now with continuous therapy, patients stay on treatment indefinitely until their disease progresses or there's another reason to stop,

such as intolerance.

Unlike fixed-duration treatment, when continuous treatment is stopped, patients often move directly to the next line of therapy as there's typically no prolonged treatment-free interval.

In my experience, sometimes progression doesn't trigger an immediate switch, such as in patients with indolent disease where we might see laboratory-based progression without clinical symptoms. So in some cases, we may continue the current therapy if it's still offering benefit and the patient is tolerating it. That said, patients don't often have a long interval between therapies.

So broadly speaking, fixed-duration therapy offers the opportunity of a treatment-free interval, while continuous therapy involves an indefinite treatment duration without planned breaks. Choosing between treatment options is dependent on the patient, disease characteristics, patient goals, and treatment tolerance.

**Dr. Turck:**
So with that in mind, let's break down what PFS and TTNT can look like in the context of each treatment strategy. Could you start us off with fixed-duration therapy?

**Dr. Davis:**
Yes, with fixed-duration therapy, PFS includes the time the patients actively on treatment *plus* the time they remain progression-free while off treatment.

For fixed-duration regimens, TTNT may extend beyond PFS. That's because even when patients meet the clinical criteria for progression—such as a rising lymphocyte count—they may remain asymptomatic and not meet the iwCLL criteria for initiating subsequent treatment. We would monitor closely but hold off on treating until there was a clear clinical need.

So while PFS tells us when disease progression occurs, TTNT reflects when additional treatment is needed.

**Dr. Turck:**
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. Carter Davis about measurement of PFS and TTNT in continuous and fixed-duration therapies for CLL.

Now, Dr. Davis, let's switch gears for a moment and talk about continuous therapy. How do we evaluate PFS and TTNT with that approach?

**Dr. Davis:**
In my experience with continuous therapy, patients who progress or need to stop treatment early because of side effects often need to switch therapy relatively soon due to disease progression and appearance of symptoms. So in this setting, PFS is spent on active therapy and the duration of PFS and TTNT are closer in time as patients generally meet criteria for treatment soon after disease progression.

**Dr. Turck:**
So when we consider these two therapeutic approaches, what should we keep in mind while evaluating PFS and TTNT?

**Dr. Davis:**
The key thing to remember is that PFS remains a commonly used primary endpoint in CLL clinical trials, as it's a well-established measure of how long a therapy can delay disease progression.

In practice, TTNT adds depth to the conversation with the patient because it describes how long a patient may have before needing to start therapy. With a fixed-duration regimen, patients have a treatment-free interval in which they're able to stay off active treatment and limit drug exposure. I'd like to share my own experience here with two patient cases.

In the first case, a 60 year-old female patient with CLL developed painful right-sided axillary lymphadenopathy. As she had symptomatic disease and met iwCLL criteria for treatment, she started a continuous therapy with improvement in her lymph nodes and reduction in pain. She continued therapy for approximately three years before having to stop due to an intolerable side effect. Within two months, she experienced another symptomatic lymph node progression and began therapy at that time. So in this example, her PFS and TTNT were nearly identical.

Let's talk about the second case, a 52 year-old female patient who developed rapid progression of lymphocytosis, which meets an indication for therapy as per iwCLL guidelines. She was treated with a fixed duration regimen for approximately one year and maintained a complete response at the end of therapy. She was then observed off therapy until about six years later, when she developed recurrent lymphocytosis with flow cytometry showing relapsing disease. She was asymptomatic, so she was able to be

closely monitored for an additional year, and then she developed weight loss which required therapy. In this example, her TTNT was longer than PFS by approximately one year.

**Dr. Turck:**
This has been a really thoughtful breakdown, Dr. Davis. Just to wrap things up, what would you want colleagues to take away from our discussion today?

**Dr. Davis:**
I'd like to emphasize that both PFS and TTNT are valuable endpoints, and we need to interpret them through the lens of treatment duration. While PFS remains a key benchmark for clinicians, I think of TTNT as a patient-centered measure because it helps describe not just when disease progression occurs, but when a new treatment decision needs to be made. That makes it valuable to include in shared decision-making, especially when discussing treatment selection between fixed-duration and continuous approaches.

When we bring both PFS and TTNT into the discussion, we can personalize care for patients.

**Dr. Turck:**
Great point, Dr. Davis, and I really appreciate your insights on how these key endpoints can differ for continuous and fixed-duration CLL treatment strategies. Thanks so much for being here today.

**Dr. Davis:**
Thank you for having me.

**Announcer Close:**
This medical industry feature was sponsored by AbbVie 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.

**References:**

1. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-2760. doi:10.1182/blood-2017-09-806398