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# Combination Therapy for CLL: What Evidence Do We Have?

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**Dr. Wierda:**
Hi, I'm Bill Wierda from the MD Anderson Cancer Center in Houston, Texas, and this is a CME event on ReachMD. And I'm going to be briefly talking about fixed-duration combination therapy for patients with chronic lymphocytic leukemia. Over the years, we have transitioned from an era of chemoimmunotherapy to targeted therapy, and in that process, we have data from a number of clinical trials that have evaluated chemoimmunotherapy versus targeted therapy. All of those trials demonstrated improved outcomes, particularly progression-free survival and in some cases, overall survival favoring treatment with targeted therapy.

Now, there's 2 general options for targeted therapy, those are maintenance strategy, where patients go on a BTK inhibitor and are maintained with extremely good disease control and remission, but not to the depth where we're comfortable with discontinuing treatment. And then the other strategy is what's called fixed-duration therapy, and that is a strategy with targeted therapy that is similar to what we've been familiar with with chemoimmunotherapy, and that is patients receive treatments to achieve a remission, and once they achieve that remission with a duration of therapy that's sufficient to get them in a deep remission, then they're able to discontinue with treatments in remission and remain in remission off treatment for an extended period of time, usually years. The initial strategy with that has been with venetoclax plus obinutuzumab. The trial that supports that has been the CLL14 trial done by the German CLL Study Group. Venetoclax is a BCL-2 small molecule inhibitor. It has been combined with a CD20 antibody in the frontline setting; that has been obinutuzumab. In the relapse setting that was with rituximab. And venetoclax was given for a year of finite-duration treatment in the frontline setting and 2 years in the relapse setting. And again, the objective of that strategy of treatment was to achieve a deep remission and get patients off treatment and in remission in follow-up.

We recently had the follow-up data from the CLL14 trial, which demonstrated a median progression-free survival of 6 years. Patients with an unmutated immunoglobulin gene have a median progression-free survival of 5 years. We don't know what the median is for patients with a mutated immunoglobulin chain. So those patients certainly have a duration of remission and progression-free survival that's lasting longer than this median of 6 years. Patients with 17p deletion or mutated TP53 had a median progression-free survival of 4 years.

So with fixed-duration, 1 year of treatment, those are very good outcomes and very durable remissions with nonchemotherapy-based treatment, which is relatively well tolerated.

Subsequent trials and subsequent efforts have gone into optimizing venetoclax-based treatment. Venetoclax plus a BTK inhibitor, venetoclax plus a BTK inhibitor plus a CD20 antibody. There are multiple trials that are evaluating venetoclax-based fixed-duration treatment, and we'll see those data coming out over the next few years. We do have data from venetoclax plus ibrutinib, or BCL-2 plus a BTK inhibitor. Those outcomes have been exceptionally good. There hasn't yet been any available data comparing a BCL-2 or

venetoclax plus a CD20 antibody versus venetoclax plus a BTK inhibitor, but we will be seeing those data coming out in the near future with the German CLL Study Group trial.

So with the current strategies to optimize therapy and particularly with attention to targeted therapy, the clinical trials and clinical development currently that's ongoing has been directed at optimizing venetoclax-based strategies, or BCL-2 inhibitor-based strategies, which, again, are finite-duration treatment and have included venetoclax or other BCL-2 inhibitors plus a BTK inhibitor with or without a CD20 antibody. And those trials have been developed with the objective of achieving the highest proportion of patients in an undetectable MRD state with the expectation that that will translate into the longest progression-free survival and potentially a cure for patients with CLL.

**Announcer:**
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