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# Fixed-Duration Therapy in the Relapsed/Refractory CLL Setting

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**Dr. Kipps:**
Hello, this is CME on ReachMD, and I'm Dr. Thomas Kipps, and I'm joined today by Dr. William Wierda of MD Anderson. And I'm here today to talk about mechanisms of resistance to therapy for chronic lymphocytic leukemia. Bill?

**Dr. Wierda:**
Hi. Thanks, Tom. So in terms of resistance and what patterns that we're seeing and what are some of the mechanisms of resistance, this is a very important topic, and particularly paying attention to targeted therapy.

The 2 treatment options and strategies we have are BTK inhibitor-based therapy, which is continuous treatment. Resistance is manifest as progression on treatment in that setting. With the covalent BTK inhibitors, the typical mechanism of resistance is acquisition of a mutation in BTK that renders the molecule unable to be bound by the covalent BTK inhibitor, in this case ibrutinib or acalabrutinib or zanubrutinib. That's the cysteine 481 amino acid of BTK, and that's very commonly seen in patients progressing on a covalent BTK inhibitor and is associated with resistance.

There is a new agent that was recently approved which is a non-covalent, or reversible, inhibitor BTK that’s pirtobrutinib. It binds to a different location on BTK, and there is activity in treating patients who have C481 mutation with pirtobrutinib where we expect a response, and those responses are durable.

With venetoclax, it's a little less clear in terms of the mechanisms, and I think there's multiple mechanisms that are in play. Patients can have upregulation or increased expression of BCL-2 and increased expression of MCL1. Mutations in BCL-2 have been reported, but that's not the predominant mechanism of resistance with venetoclax. And so I think that’s still an area of study, and aggressive study, to understand what are the reasons why patients develop resistance to venetoclax. Venetoclax is finite- or fixed-duration treatment, so typically we don't see patients with progression while on venetoclax; it's after they've completed their fixed-duration treatment with venetoclax. And when the disease recurs, the question is, can we use venetoclax as a reasonable option with an expectation of a response when we re-treat after that, in the setting of having had prior venetoclax. And the duration of remission sort of gives some insights into the answer to that question.

**Dr. Kipps:**
Now you mentioned the 2 major categories, of course, the covalent BTK inhibitors and now, more recently, the non-covalent BTK inhibitors. But there's a new category that's being evaluated now, the BTK degraders. Do you care to talk on that?

**Dr. Wierda:**
We don't have any data yet on activity of the degraders in patients who have C481 mutation or a 528 or 474 mutation, which are the

ones that are seen on the inhibitors. The degraders also require binding to BTK and the mechanism of resistance in that setting, whether we're talking about an inhibitor or a degrader, is for the protein to mutate as a way to avoid the mechanism of action of that drug. So I do anticipate that we will see activity with degraders in patients who develop resistance on the inhibitors, whether they be covalent or non-covalent. But I also anticipate that by virtue of how the cells work and how the cells develop resistance, we will probably see a resistance mechanism to the degrader being mutation in BTK. But that's speculation and we wait to see if there's data that substantiates that.

**Dr. Kipps:**
Well, that may be. Our time is up, unfortunately. That's a great discussion that we had, Dr. Wierda, and I thank you for leading it and also thank our audience for tuning in. So thank you very much.

**Announcer:**
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