# Blood Cancer Video Library

## CLL (Chronic Lymphocytic Leukemia) – A New Generation of BTK Inhibitors

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Dr. Joshua Brody: Hi, my name is Josh Brody. I am the director of the Lymphoma Immunotherapy Program at the Icahn school of medicine at Mount Sinai here in New York. At the recent annual ASH 2019 meeting for the American society of hematology. It was just held in early December. We had a lot of exciting updates, but perhaps amongst the most exciting for patients with a very common type of leukemia called CLL. Chronic lymphocytic leukemia, were a number of clinical trials that are ongoing for a new type of medicine which is really a sort of a version 2.0 of a class of medicines that has already made a huge change in how we take care of these patients with CLL. So the class of medicines are called BTK inhibitors. The first FDA approved BTK inhibitor was called ibrutinib and ibrutinib. And then some subsequent versions of BTK inhibitors called acalibrutinib and zanabrutinib have had a huge impact on how we take care of these patients.

In fact most commonly when patients are diagnosed with this type of leukemia they're frequently not treated with chemotherapy as the first therapy. Frequently, they are treated with these BTK inhibitors, these pills, which are pretty well tolerated and people take them and they generally put their CLL into remission for years. We've had patients taking ibrutinib and other BTK inhibitors for six, seven, eight years, still in remission, and these pills are pretty well tolerated. It's, you know, we say not that different than taking your blood pressure pill or cholesterol pill every day. People are taking these CLL pills

every day for years with mostly no side effects and the majority of patients going into remission and staying into remission for a long time. So that's wonderful because those patients get to sometimes avoid some of the side effects of chemotherapy, which for some patients is definitely preferable. Chemotherapy is still an option for patients with CLL, but the majority of patients opt to get treated with these targeted therapies, the BTK inhibitors.

The new updates which we're getting more information now, especially at this ASH 2019 meeting are that sometimes times these BTK inhibitor pills stop working after in some patients months or many, many years. And one reason that the patients CLL might sort of outsmart these medicines is the patient's CLL cells learn how to literally take the target of the medicine, this molecule called BTK and push the inhibitor, push the medicine out away from that target. So the BTK actually mutates in a way to protect itself from that medicine. And it's sort of very scary that it's able to do that, but also very elegant that a bunch of physicians and scientists were able to figure out that's why the medicine was no longer working. And because they figured it out, they've now developed a whole new version 2.0 group of these BTK inhibitors, which are able to bind an attack that target that protein called BTK inside of the CLL cells. Even when the original versions, the ibrutinib and the calibrutinib medicines were not able to bind and to ongo the patients remission.

So these new BTK inhibitors as a class, they have a name called reversible BTK inhibitors, whereas the old medicines were called irreversible BTK inhibitors. And what's exciting about them is we're finally just at this year's ASH meeting, starting to see that patients treated with these reversible BTK inhibitors. And there are about three examples that were updated in recent to ongoing clinical trials. One from a company called Arquel, one from a company called Loxo, and one from a company called Sunesys. And all of these have developed reversible BTK inhibitors that are being tried in patients with CLL and also some other types of lymphomas and leukemias. And we're seeing that these patients are just as we hoped, even though sometimes the brutinib, and calibrutinib, those old BTK inhibitors were not working, that these reversible. BTK inhibitors have been working and patients have gone into partial and complete remissions.

So that's very exciting for us, especially because these new versions of the BTK inhibitors seem to be pretty well tolerated and most patients are not having any significant side effects. So that's very exciting because BTK inhibitors as a class completely changed the way that we treat patients with CLL. And this has been one little weakness of that class. The ability of some patients, CLL cells to push those BTK inhibitors out of the groove, out

of the place where they bind to the target. And in this new class of medicines seems to still be able to inhibit the target inside those CLL cells cause CLL cells to melt away and put those patients into remission. Very exciting and very elegant and promising new clinical update on those reversable BTK inhibitors at this recent meeting. So a big deal for our patients with CLL. Big deal for all of us.