



Targeted oral treatment options for chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are medications taken by mouth that identify and attack specific cancer cells. They are designed to specifically target certain molecules, proteins, enzymes, or pathways that are known to be involved in the growth and survival of certain cancer cells. When it is time to start treatment, a targeted oral treatment option is often one of the first medications selected to treat the disease.

## ARE TARGETED ORAL TREATMENT OPTIONS THE SAME AS CHEMOIMMUNOTHERAPY?

No, they are quite different. Unlike chemo-immunotherapy, which typically attacks all rapidly dividing cells throughout the body including healthy ones, targeted therapy selectively blocks certain cancer cells from continuing to replicate and grow while minimizing harm done to healthy cells. By targeting only cancerous cells, the result is fewer side effects compared to chemoimmunotherapy.

## WHEN AND HOW ARE TARGETED ORAL TREATMENT OPTIONS NORMALLY USED?

They can be utilized the very first time a treatment is needed (also called front-line therapy), or they can be used later as a subsequent line of therapy. There are various targeted oral treatment options available for those living with CLL and SLL which can be used alone or in combination with other types of treatments.

## HOW EXACTLY DO TARGETED ORAL TREATMENT OPTIONS WORK?

These drugs interfere with specific proteins or pathways critical for the survival and growth of CLL and SLL cells, by slowing or stopping their growth.

## WHAT TYPES OF TARGETED ORAL TREATMENT OPTIONS ARE FDA-APPROVED FOR CLL AND SLL?

The drug classes approved to treat CLL include:

- **Bruton Tyrosine Kinase (BTK) Inhibitors:** BTK inhibitors play a crucial role in managing the disease. BTK is an enzyme that plays a pivotal role in activating B-cell receptor (BCR) signaling. BCR signaling is essential for both normal B-cell development and the survival of cancerous B-cells. BTK inhibitors work by blocking the BTK enzyme, and by doing so it reduces the growth of cancerous B-cells and promotes their death. There are two types of BTK inhibitors, covalent and non-covalent. Covalent BTK inhibitors bind irreversibly to a target called C481, leading to prolonged inhibition of BTK activity. Currently, FDA-

approved BTK covalent inhibitors include ibrutinib, acalabrutinib, and zanubrutinib. The non-covalent BTK inhibitor, pirtobrutinib, is also used to treat the disease. Due to the way it uniquely engages in a reversible way with BTK, it reduces the potential for adverse side effects, and it can still be used to treat the disease even when the cancer has become resistant to one of the covalent BTK inhibitors.

- **B-Cell Lymphoma-2 (BCL-2) Inhibitors:** BCL-2 is a protein within cells that plays a critical role in regulating the death of cells. In CLL and SLL, the cancerous B-cells tend to produce an excessive amount of the BCL-2 which helps the malignant cells survive longer than they should. BCL-2 inhibitors target this protein and inhibit its survival pathway, causing the cancerous cells to die. The only BCL-2 inhibitor that is currently FDA-approved for the disease is Venetoclax. It is given for a limited amount of time, and it may be administered in combination with other medications (such as the anti-CD20 monoclonal antibody drugs rituximab or obinutuzumab) to increase the effectiveness.
- **Phosphoinositide 3-Kinase (PI3K) Inhibitors:** PI3K is another signaling pathway that regulates various cellular processes. PI3Ki medications target this pathway and inhibit the activity of the PI3K enzyme. This reduces the growth and survival of cancerous cells and ultimately leads to their death. FDA-approved PI3K inhibitors include idelalisib and duvelisib. Due to the severe adverse side effects associated with this type of therapy, PI3K inhibitors should never be the first choice of treatment. Instead, they are often considered as an alternative later option for people with CLL and SLL who do not respond (or stop responding) to other types of treatments.

## WHAT ARE THE ADVANTAGES OF TARGETED ORAL TREATMENT OPTIONS?

Targeted oral therapies have revolutionized the treatment landscape for disease and offer several advantages over traditional approaches like chemoimmunotherapy. They are highly effective



# TARGETED ORAL TREATMENT OPTIONS (continued)

for most people living with the disease and are currently the standard of care when treatment is necessary. Because of the targeted action against cancerous cells, there is a reduced risk of the side effects that are commonly associated with chemoimmunotherapy. This leads to an improved quality of life. These medications come in pill (or liquid) form, which allows for them to be taken by mouth at home and eliminates the need to travel to a clinic or infusion center. Additionally, clinical trials have proven that these targeted oral treatments result in longer survival times compared to chemoimmunotherapy.

## ARE THERE ANY DISADVANTAGES OF TARGETED ORAL TREATMENT OPTIONS?

Like any medication, oral treatments can cause side effects. When taking oral medications, their effectiveness is highly dependent upon taking the medication exactly as prescribed. Targeted oral therapies require strict adherence to the recommended schedule. While these treatments may be more convenient compared to intravenous (IV) treatments that require going to a healthcare provider's office or infusion clinic, oral medications can be very expensive, and managing the costs may be very challenging for some.

## HOW LONG DO PEOPLE NEED TO TAKE THESE TYPES OF MEDICATIONS?

BTK inhibitors and PI3K inhibitors must be taken continuously until severe adverse side effects (drug toxicities) develop that cannot be tolerated or until the disease progresses while on the medication. BTK inhibitors control the disease but do not eliminate it. Over time, the cancerous cells can develop mutations that make covalent BTK inhibitors ineffective. When this happens, it will be necessary to switch to another treatment option that is not a covalent BTK inhibitor. This is because if an individual has become resistant to one of the non-covalent BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib), the others within that same drug class will not work either. The BCL-2 inhibitor venetoclax is taken for a pre-determined length of time (called time-limited therapy) since it doesn't just control the cancer, it can result in deep remissions. When it is taken by someone who has never undergone treatment before it is usually administered for one year. When it is taken by someone who has undergone treatment before whose cancer has relapsed or become refractory to

the treatment they were previously on, it is usually administered for two years. After discontinuation of venetoclax, continued close monitoring is crucial to detect disease recurrence.

## CAN TARGETED ORAL TREATMENT OPTIONS CURE THE DISEASE?

These therapies significantly improve outcomes for those living with the disease, but none provide a definitive cure. They can, however, be highly effective at controlling the cancer and prolonging survival. Some do achieve deep remissions for many years, but responses are highly variable. CLL and SLL remain a chronic condition, so many people receive treatment off and on many times throughout their lives whenever the cancer becomes active and worsening symptoms appear.

## HOW DO I KNOW WHICH TARGETED ORAL TREATMENT OPTION MIGHT BE BEST FOR ME?

Disease management of CLL and SLL is multifaceted, and it is a very personalized decision. The choice of therapy depends on many factors. One of these important factors is the individual disease characteristics that are only understood by undergoing biomarker testing. Before starting any new treatment, it is crucial to perform FISH and TP53 testing even if you have had them performed before. This is because these two biomarkers can change with time. Additionally, you should know your IGVH mutational status. This test generally does not change over time, so it only needs to be performed once. The results of these tests can help your healthcare provider know if certain treatments will be effective or not in treating your type of the disease.

Another factor that should be considered is what are your treatment goals. For example, do you prefer to take a daily medication continuously or would you rather take a medication for a limited duration of time? Your healthcare provider will also take into consideration your overall health status and previous treatment history when discussing what treatments might be best for you. Financial considerations might also be a determining factor when selecting a targeted oral treatment option. The decision to move forward with any treatment regimen is very personal and should only take place after considering all the potential benefits and risks that might be associated with each approach.