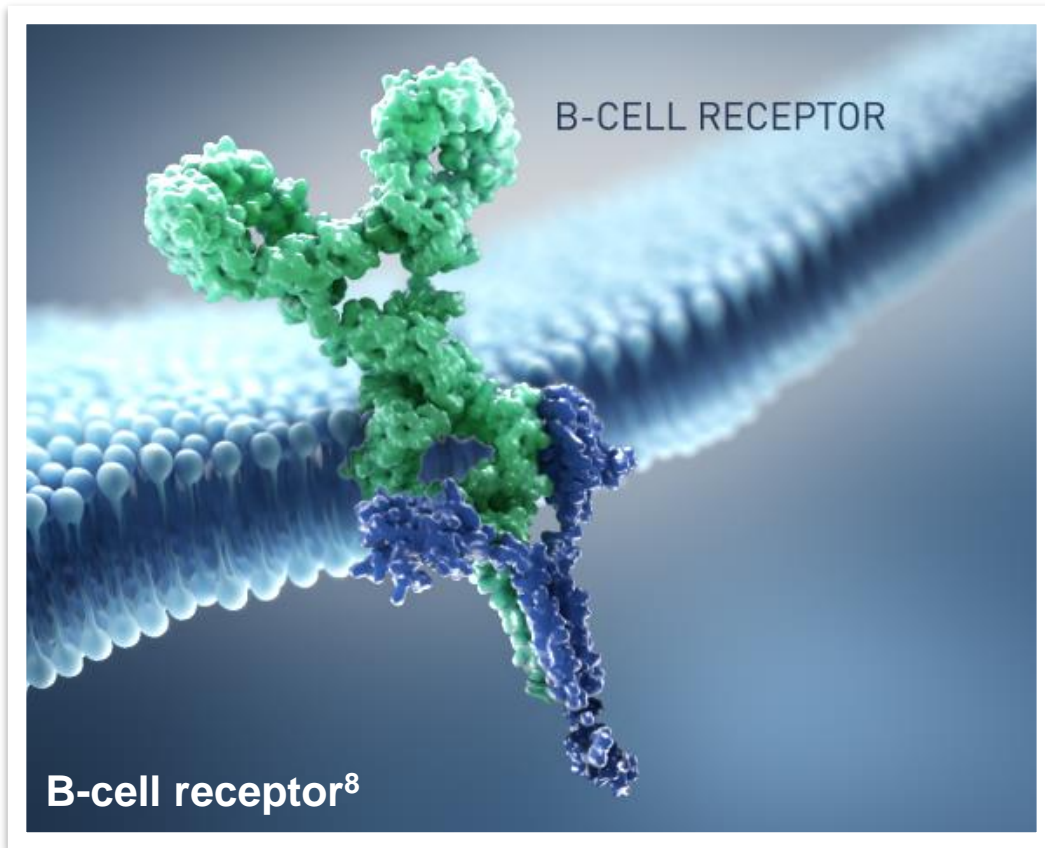


# Understanding Bruton's Tyrosine Kinase Pathway Inhibition in B-Cell Malignancies

# BCR Signaling Pathway Plays a Critical Role in B-Cell Malignancies<sup>1-3</sup>



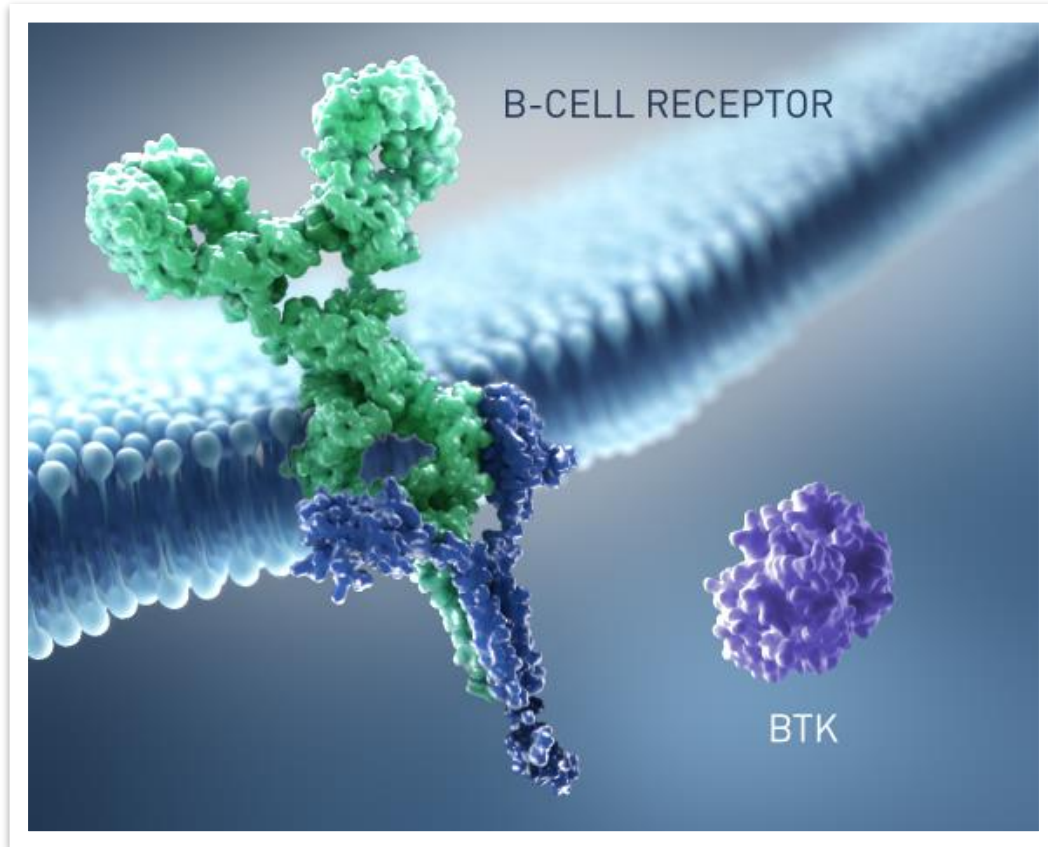
- Normal B-cell maturation and survival depends on **functional BCR signaling**<sup>4,5</sup>
- Activated B cells are **more likely to proliferate** in response to BCR signaling<sup>5-7</sup>
- BCR signaling also plays a crucial role in the **survival, proliferation, and trafficking** of malignant B cells<sup>1-3</sup>

BCR=B-Cell Receptor.

1. Sedlarikova L, et al. *Front Oncol.* 2020;10:894. 2. Hendriks RW, et al. *Nat Rev Cancer.* 2014;14(4):219-232. 3 Bosch F, et al. *Nat Rev Clin Oncol.* 2019;16(11):684-701. 4. Yam-Puc JC, et al. *F1000Res.* 2018;7:429.

5. Liu W, et al. *Front Immunol.* 2020;11:4. 6. Patterson HC, et al. *Immunity.* 2006;25(1):55-65. 7. Wen Y, et al. *Blood Sci.* 2019;1(2):119-129. 8. Treanor B. et al. *Immunology.* 2012;136(1):21-27.

# Activation of BTK Drives Proliferation of Malignant B Cells<sup>1,2</sup>

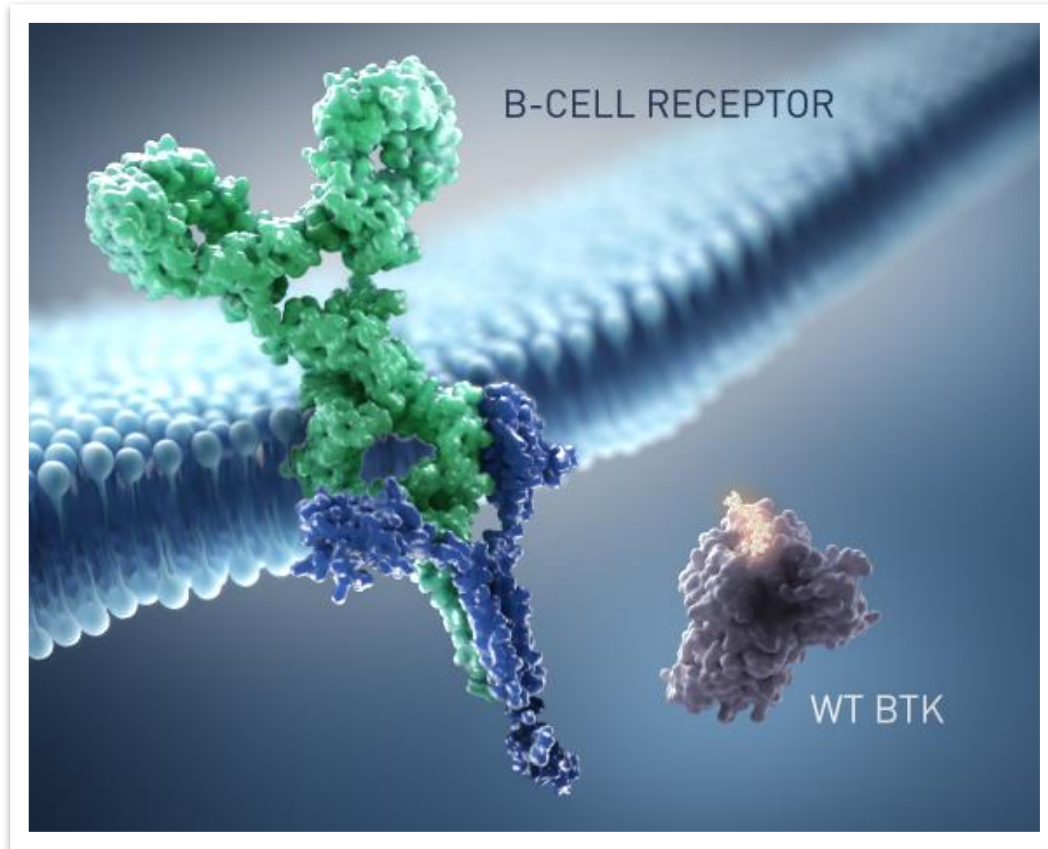


- **BTK** is a key component of B-cell development and survival acting via the BCR signaling pathway<sup>1,3,4</sup>
- Activation of the BTK pathway plays an important role in the pathophysiology of many B-cell lymphomas<sup>1,2,4</sup>

BCR=B-cell Receptor; BTK=Bruton's Tyrosine Kinase.

1. Hendriks RW, et al. *Nat Rev Cancer*. 2014;14(4):219-232. 2. Pal Singh S, et al. *Mol Cancer*. 2018;17(1):57. 3. Estupiñán HY, et al. *Front Cell Dev Biol*. 2021;9:630942. 4. Gu D, et al. *J Hematol Oncol*. 2021;14(1):40.

# Inhibition of BTK Blocks BCR Signaling<sup>1-3</sup>

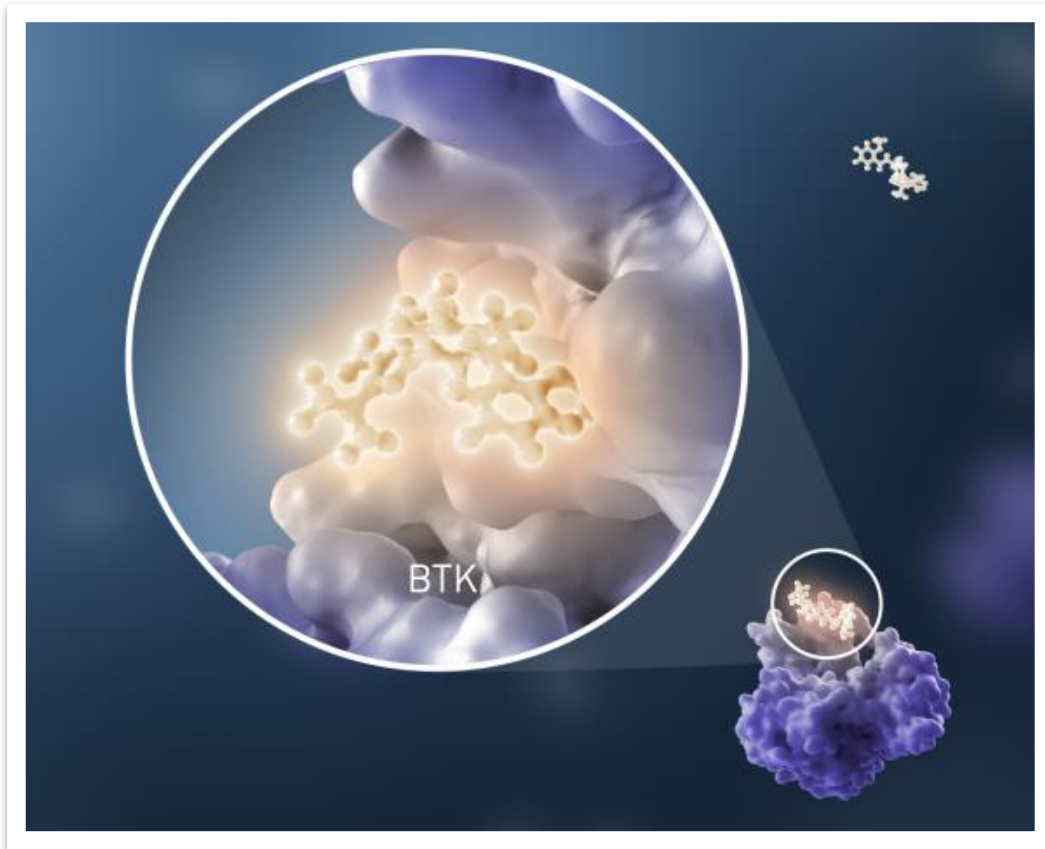


- Inhibition of BTK **disrupts ATP binding**, permanently blocking downstream enzyme phosphorylation and activation<sup>1,2</sup>
  - Blockade of BCR signaling reduces B-cell survival, proliferation, and migration<sup>2,3</sup>

ATP=Adenosine Triphosphate; BCR=B-Cell Receptor; BTK=Bruton's Tyrosine Kinase; WT=Wild Type.

1. Estupiñán HY, et al. *Front Cell Dev Biol.* 2021;9:630942. 2. Gu D, et al. *J Hematol Oncol.* 2021;14(1):40. 3. Hendriks RW, et al. *Nat Rev Cancer.* 2014;14(4):219-232.

# Covalent BTK Inhibition

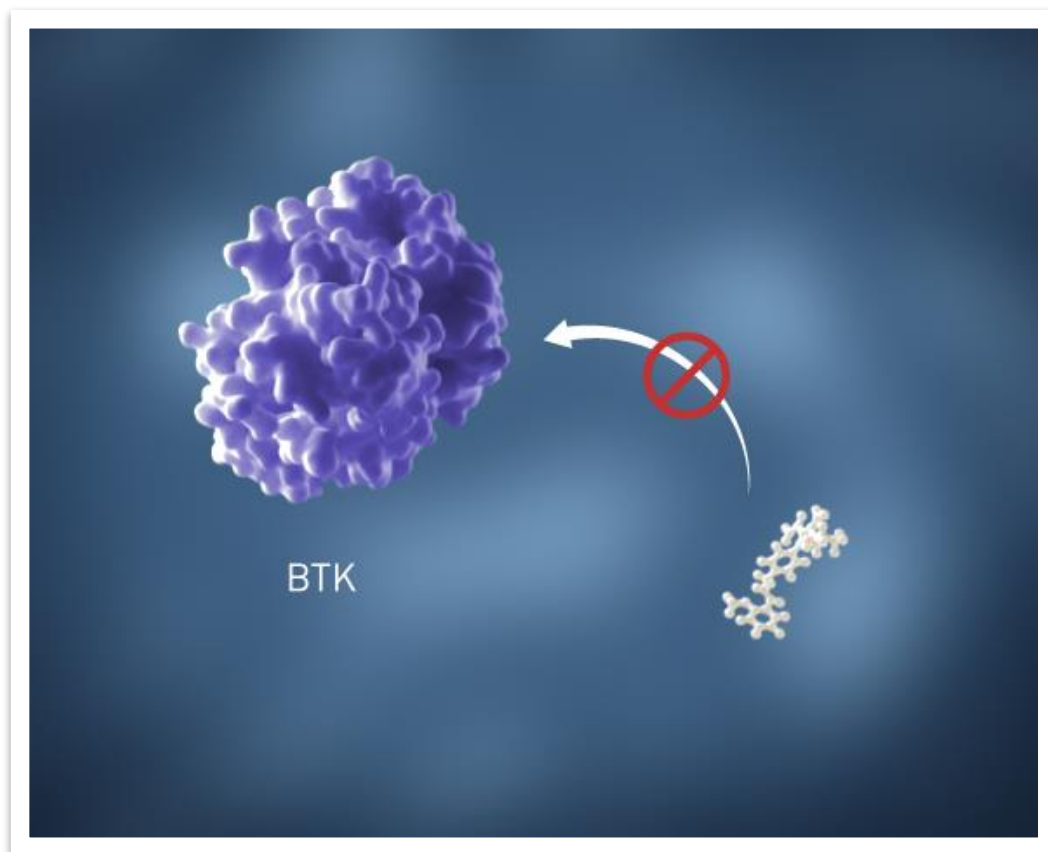


- Covalent BTK inhibition has been an important advancement in the treatment of B-cell malignancies<sup>1,2</sup>
- Inhibition of BTK often relies on a covalent, or irreversible, bond at the C481 amino site residue of the BTK protein<sup>1,2</sup>
  - To re-establish BCR signaling, cells must resynthesize new BTK
- However, changes to the BTK protein or the B-cell signaling pathway may limit covalent binding<sup>3</sup>

BCR=B-Cell Receptor; BTK=Bruton's Tyrosine Kinase; C=Cysteine.

1. Estupiñán HY, et al. *Front Cell Dev Biol.* 2021;9:630942. 2. Gu D, et al. *J Hematol Oncol.* 2021;14(1):40. 3. Alsadhan A, et al. *Clin Cancer Res.* 2020;26(12):2800-2809.

# B-Cell Malignancies Can Develop Resistance to BTK Inhibition<sup>1,2</sup>

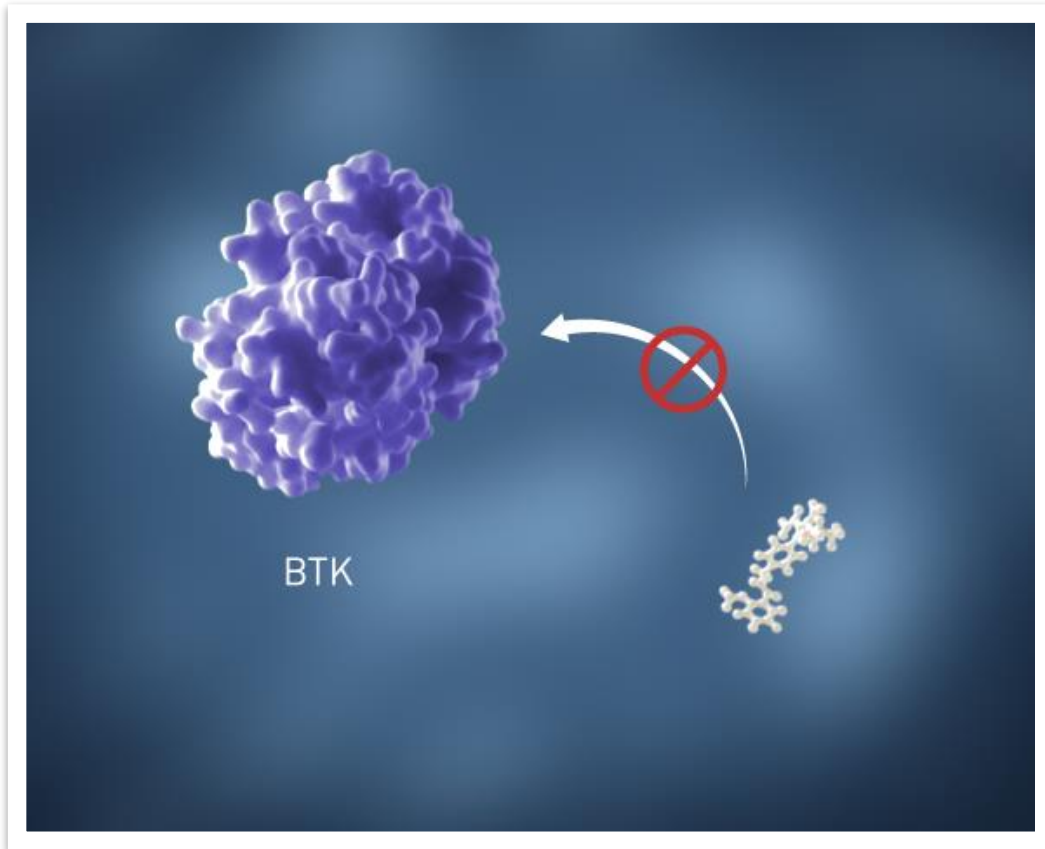


- Predominant resistance mechanisms to covalent inhibition of BTK differ depending on the type of B-cell malignancy and are not completely understood<sup>1</sup>
  - Acquired mutations in the *BTK* gene appear to be a leading mechanism for resistance to BTK inhibition in CLL<sup>1,2</sup>
  - Other proposed resistance mechanisms in CLL include genomic and epigenetic activation of parallel or downstream signaling pathways<sup>1,2</sup>
  - MCL resistance mechanisms are still being characterized<sup>3</sup>

BTK=Bruton's Tyrosine Kinase; CLL=Chronic Lymphocytic Leukemia; MCL=Mantle Cell Lymphoma.

1. Lewis KL, et al. *J Pers Med.* 2021;11(8):764. 2. Wang E, et al. *N Engl J Med.* 2022;386(8):735-743. 3. George B, et al. *Cancers (Basel).* 2020;12(5):1328.

# Resistance to Covalent BTK Inhibition Is a Growing Unmet Need<sup>1-3</sup>

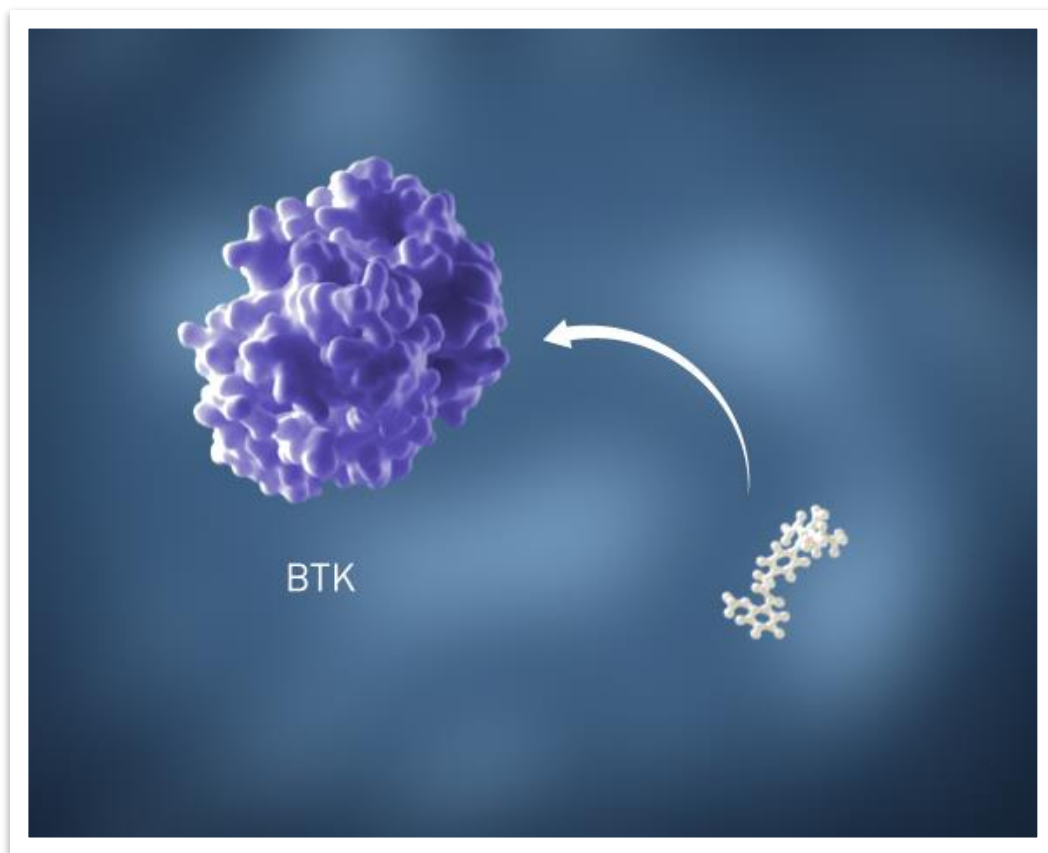


- When resistance to covalent BTK inhibition occurs, signaling through the BCR pathway can restart, potentially leading to increased proliferation of malignant B cells and relapse<sup>4</sup>
- B-cell malignancies that have relapsed due to resistance to BTK inhibition can be aggressive and resistant to further covalent inhibition<sup>2,5</sup>

BCR=B-Cell Receptor; BTK=Bruton's Tyrosine Kinase.

1. Lewis KL, et al. *J Pers Med*. 2021;11(8):764. 2. Cheah CY, et al. *Ann Oncol*. 2015;26(6):1175-1179. 3. Martin P, et al. *Blood*. 2016;127(12):1559-1563. 4. Ondrisova, et al. *Front Oncol*. 2020;10:591577. 5. Jain P. *Blood*. 2015;125(13):2062-2067.

# Continuing the Blockade of BTK May Be Possible<sup>1-4</sup>



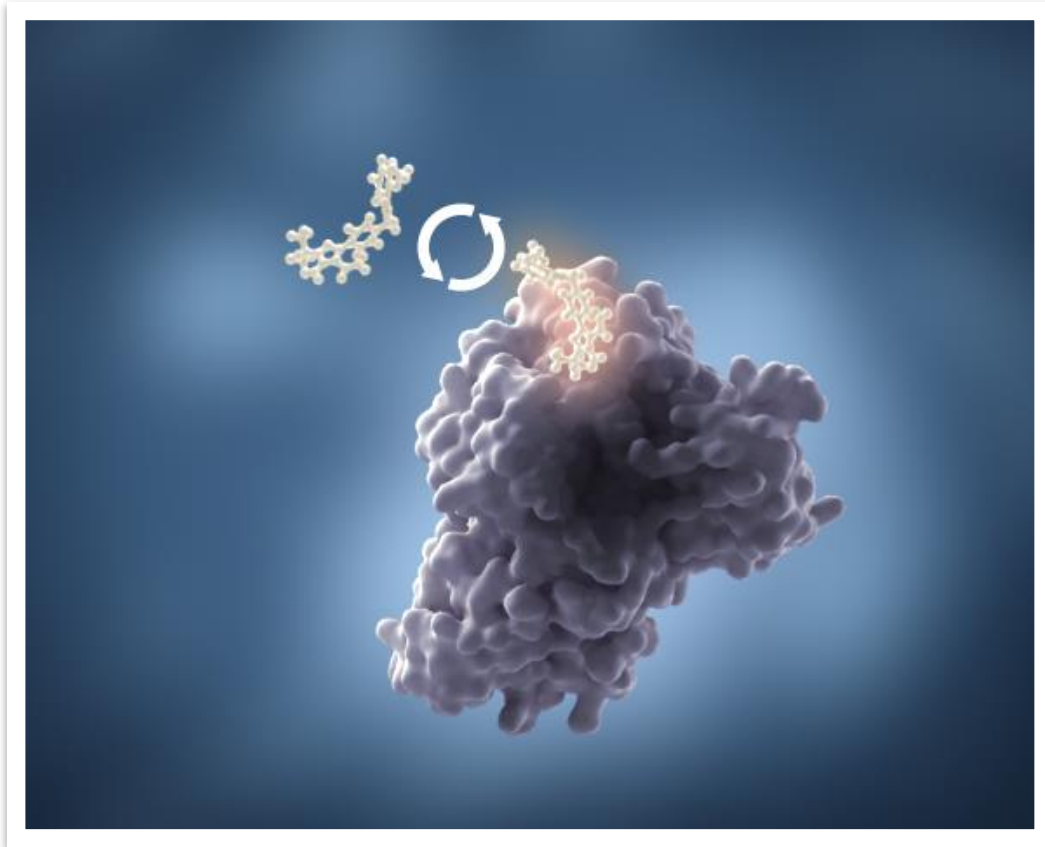
- Preclinical research suggests that the BTK pathway **may still be accessible** even when covalent BTK inhibition is no longer recommended<sup>1-4</sup>

BTK=Bruton's Tyrosine Kinase.

1. Profitós-Pelejà N, et al. *Cancers (Basel)*. 2022;14(4):860. 2. Lewis KL, et al. *J Pers Med*. 2021;11(8):764. 3. Gu D, et al. *J Hematol Oncol*. 2021;14(1):40. 4. Estupiñán HY, et al. *Blood Adv*. 2020;4(11):2439-2450.



# Non-covalent (Reversible) Inhibition Acts by Different Mechanisms to Covalent Inhibition<sup>1-4</sup>



- Inhibition that is non-covalent, or reversible, may offer a potential option for patients who develop acquired resistance to covalent inhibition<sup>1-4</sup>

1. Profitós-Pelejà N, et al. *Cancers (Basel)*. 2022;14(4):860. 2. Lewis KL, et al. *J Pers Med*. 2021;11(8):764. 3. Gu D, et al. *J Hematol Oncol*. 2021;14(1):40. 4. Estupiñán HY, et al. *Blood Adv*. 2020;4(11):2439-2450.