Sequencing BTK inhibitors in the Treatment of B-Cell Malignancies

CHRONIC LYMPHOCYTIC LEUKEMIA

Role of ncBTKis in the Treatment of CLL

- ncBTKis bind **reversibly** to the BTK protein, which may address certain limitations of acquired resistance that occur with cBTKis[1,2]
- ncBTKis may provide an option for patients with CLL requiring treatment after failure on **both** a cBTKi and BCL-2i[2]

Evidence-Based Approach to Sequencing BTKis in CLL

1L Therapeutic options include

- Covalent BTKi ± anti-CD20 mAb
- BCL-2i + anti-CD20 mAb

Prior covalent BTKi ± anti-CD20 mAb only

Prior BCL-2i ± anti-CD20 mAb only

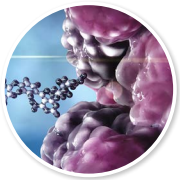
Randomized data on the optimal 1L treatment are lacking, though comparative trials are ongoing (eg, CLL17, MAJIC). Selection of 1L treatment relies on individualized patient-clinician decision-making[3-6]

Discontinuation due to progression

Mutations conferring resistance to cBTKis or BCL-2is can develop, resulting in progression; switching to the class of agent not used in the 1L setting is a common sequencing strategy (for example, cBTKi → BCL-2i and vice versa)[1,7]

BCL-2i ± anti-CD20 mAb

Covalent BTKi



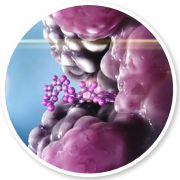
COVALENT BTKi (irreversible)

Mutations in the C481 residue of the BTK ATP binding site can diminish covalent inhibition of BTK; therefore, retreating with a cBTKi upon progression on a cBTKi is not recommended[2,7,8]

Prior sequential covalent BTKi and BCL-2i

Patients previously treated with a cBTKi, and BCL-2i may be faced with acquired resistance that can make selecting the next line of therapy more challenging[1,7]

Non-covalent BTKi*



NON-COVALENT BTKi (reversible)

Non-covalent binding can overcome the effects of C481 mutations to allow continued BTK inhibition and restoration of blockade of B-cell signaling[8]

*CD19-directed CAR T-cell therapy is also an approved treatment option in this setting.[9]

1L, first line; ATP, adenosine triphosphate; BCL-2i, B-cell lymphoma 2 inhibitor; BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; cBTKi, covalent BTK inhibitor; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; mAb, monoclonal antibody; ncBTKi, non-covalent BTK inhibitor.

References: 1. Mato AR, et al. *Clin Cancer Res*. 2022;28(4):603-608. 2. Montoya S, Thompson MC. *Cancers (Basel)*. 2023;15(14):3648. 3. Hallek M, Al-Sawaf O. *Am J Hematol*. 2021;96(12):1679-1705. 4. Ahn IE, Brown JR. *Hematology Am Soc Hematol Educ Program*. 2022(1):323-328. 5. ClinicalTrials.gov identifier: NCT04608318. Updated March 6, 2024. https://clinicaltrials.gov/ct2/show/NCT04608318. 6. ClinicalTrials.gov identifier: NCT05057494. Updated December 6, 2024. https://clinicaltrials.gov/study/NCT05057494. 7. Fresa A, et al. *Cancers (Basel)*. 2024;16(11):2011. 8. Mato AR, et al. *N Engl J Med*. 2023;389(1):33-44. 9.Targeted Oncology. Accessed November 11, 2024. https://www.targetedonc.com/view/fda-approves-liso-cel-in-relapsed-or-refractory-cll-sll.

Sequencing BTK inhibitors in the Treatment of B-Cell Malignancies

MANTLE CELL LYMPHOMA

Role of ncBTKis in the Treatment of MCL

- Despite initial efficacy of cBTKis in R/R MCL, resistance or intolerance invariably develops, necessitating a new treatment option[1,2]
- ncBTKis have key differences in structure and MOA compared with cBTKis, including **reversible** binding[1,2]
- ncBTKis may address some of the limitations of resistance cBTKis pose[3]

Evidence-Based Approach to Sequencing BTKis in MCL

1L Therapeutic options include

- Aggressive CIT regimen with ASCT
- Less aggressive CIT with or without ASCT

Aggressive CIT followed by ASCT and maintenance immunotherapy

Less aggressive CIT followed by ASCT (if tolerated) and maintenance immunotherapy

1L SOC includes an aggressive or less aggressive CIT regimen with or without ASCT depending on patient age and fitness followed by maintenance immunotherapy once remission is reached[3,4,†]

Relapsed/refractory

Patients will eventually progress following 1L treatment; cBTKis are SOC for R/R MCL[3,4]

Covalent BTKi

- Eventually, resistance develops in most patients exposed to cBTKis[4]
- In MCL, mechanisms of resistance are less well understood but may involve both genetic or epigenetic processes that collectively restore BTK signaling (activation of alternative pathways or increased BTK turnover)[2,5,6]

Relapsed/refractory

Non-covalent BTKi*

Through differences in pharmacological, biophysical, and structural attributes, ncBTKis have been shown to reestablish BTK inhibition in patients with MCL who have progressed on a cBTKi[2,4-6]

*CD19-directed CAR T-cell therapy is also an approved treatment option in this setting.[7]

†No regimen has been firmly established as SOC.

1L, first-line; ASCT, autologous stem cell transplant; BTKi, Bruton's tyrosine kinase inhibitor; CAR, chimeric antigen receptor; cBTKi, covalent BTK inhibitor; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MOA, mechanism of action; ncBTKi, non-covalent BTKi; R/R, relapsed/refractory; SOC, standard of care.

References: 1. Lewis KL, Cheah CY. *J Pers Med*. 2021;11(8):764. 2. Wang ML, et al. *J Clin Oncol*. 2023;41(24):3988-3997. 3. Jain P, Wang ML. *Am J Hematol*. 2022;97(5):638-656. 4. Jain N. *J Hematol Oncol*. 2023;16(1):99. 5. Gomez EB, et al. *Blood*. 2023;142(1):62-72. 6. Stanchina MD, et al. *Nat Rev Clin Oncol*. 2024;21(12):867-887. 7. FDA. Accessed November 20th, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lisocabtagene-maraleucel-relapsed-or-refractory-mantle-cell-lymphoma.