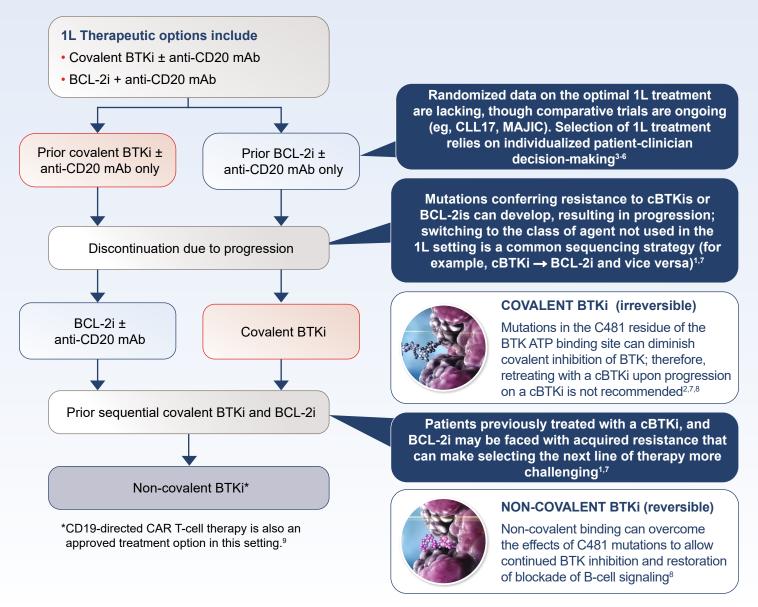
Role of ncBTKis in the Treatment of CLL

CHRONIC LYMPHOCYTIC LEUKEMIA

- 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-2i²

Evidence-Based Approach to Sequencing BTKis in CLL



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.

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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 pose³ 	
1L Therapeutic op • Aggressive CIT re	tions include	to Sequencing BTKis in CLL It 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.†}
Relaps	ed/refractory	Patients will eventually progress following 1L treatment; cBTKis are SOC for R/R MCL ^{3,4}

• Eventually, resistance develops in most patients exposed to cBTKis⁴

 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}

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}

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.

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Covalent BTKi

Relapsed/refractory

Non-covalent BTKi*

*CD19-directed CAR T-cell therapy is also an

approved treatment option in this setting.7

[†]No regimen has been firmly established as SOC.