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Switching from Covalent BTKi to BCL2i is Associated with Improved Clinical Outcomes Compared to Switching to a Different Covalent BTKi in Patients with CLL/SLL Treated in the Real-world Setting

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OBJECTIVE

To assess real-world treatment outcomes of patients with CLL/SLL who switched to a cBTKi- or a BCL2i-based regimen following discontinuation of a cBTKi-based regimen

CONCLUSIONS

Patients who switched from a cBTKi to a BCL2i-based regimen had significantly greater odds of responding to therapy, a significantly lower hazard of progression/death, and a trending lower hazard of starting next treatment /death compared to those who switched to cBTKi-based regimens

This study provides real-world evidence supporting the effectiveness of BCL2i-based regimens in improving treatment outcomes post cBTKi-based regimens compared to sequencing through cBTKis

In light of the dynamic CLL treatment landscape, it is vital to consider the impact of switching to agent(s) with a different MOA versus retreating with agent(s) in the same class as a means of optimizing clinical care

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CORE

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INTRODUCTION

- Covalent Bruton tyrosine kinase (cBTKi) and B-cell lymphoma 2 (BCL2i) inhibitors have demonstrated improved treatment efficacy and safety compared to chemotherapy/chemoimmunotherapy (CT/CIT) for patients with chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL)[1-3]
- Although some patients progress and discontinue their cBTKi-based regimens prematurely (12-17%), a substantial proportion (24-62%) discontinue due to reasons other than disease progression (PD) and often switch to another targeted agent with the same or different mechanism of action (MOA)[4-9]

METHODS

- Data were obtained as part of the CLL Collaborative Study of Real-World Evidence (CORE), an international, retrospective observational study involving 23 centers
- Adult patients were included if they were diagnosed with CLL/SLL, were naïve to BCL2i, discontinued their first treatment with a cBTKi-based regimen in any line of therapy for reasons other than PD or therapy completion, and initiated a cBTKi or BCL2i-based regimen after their first cBTKi-based regimen discontinuation. Then, 2 mutually exclusive cohorts were derived based on the treatments these patients received: cBTKi cohort (i.e., cBTKi→cBTKi) or BCL2i cohort (i.e., cBTKi→BCL2i)
- Treatment outcomes included overall response (OR; i.e., complete [CR] or partial response [PR]), progression-free survival (PFS; i.e., time from initiation to PD/death (event), with censoring at last follow-up), and time to next treatment or death (TTNT-D; i.e., time from initiation to start of next treatment/death (event), with censoring at last follow-up)
- Logistic regression models assessed the odds of achieving an OR; Cox proportional hazards (PH) regressions assessed PFS and TTNT-D
  - All models controlled for age at initiation, sex, time from CLL/SLL diagnosis to initiation, duration of discontinued cBTKi therapy, ECOG, and lactate dehydrogenase (LDH)
- Kaplan-Meier (KM) estimates were also used to estimate PFS and TTNT-D rates at 12 months

RESULTS

Patient characteristics

- The study included 121 BCL2i-naïve patients who discontinued their first cBTKi-based regimen; of them, 44 patients (36.4%) switched to a cBTKi- (cBTKi cohort) and 77 patients (63.6%) to a BCL2i-based regimen (BCL2i cohort)
- Patients in both cohorts had similar characteristics, such as median age at initiation (cBTKi: 71.5 years, BCL2i: 69.0 years), male sex (cBTKi: 63.6%, BCL2i: 68.8%), unmutated IGHV (cBTKi: 47.7%, BCL2i: 37.7%), and with del(17p)/TP53 mutation (cBTKi: 20.5%, BCL2i: 27.3%) (**Table 1**)
- However, the cBTKi cohort had a greater proportion of patients with ECOG Performance Status 0 (cBTKi: 50.0%, BCL2i: 27.3%) and a lower proportion with elevated LDH (cBTKi: 29.5%, BCL2i: 46.8%)

Table 1. Demographic characteristics for the cBTKi and BCL2i cohorts

Patient characteristics	cBTKi N = 44	BCL2i N = 77	p-value
Age at cBTKi or BCL2i initiation (years), Mean± SD [Median]	70.2 ± 9.2 [71.5]	68.7 ± 9.6 [69.0]	0.41
Male sex, N (%)	28 (63.6)	53 (68.8)	0.56
Race, N (%)			0.98
White	36 (81.8)	63 (81.8)	
Other	6 (13.6)	10 (13.0)	
Comorbidities			
Cardiovascular condition	23 (52.3)	38 (49.4)	0.76
Endocrine/metabolic condition	14 (31.8)	19 (24.7)	0.40
Musculoskeletal condition	9 (20.5)	7 (9.1)	0.08
Renal condition	6 (13.6)	16 (20.8)	0.33
Neurologic condition	6 (13.6)	9 (11.7)	0.75
Respiratory condition	5 (11.4)	10 (13.0)	0.79
Rai staging, N (%)			0.98
Stage 0	5 (11.4)	9 (11.7)	
Stage I - IV	28 (63.6)	50 (64.9)	
ECOG, N (%)			0.03*
Grade 0	22 (50.0)	21 (27.3)	
Grade 1 - 3	14 (31.8)	42 (54.5)	
Unmutated IGHV, N (%)	21 (47.7)	29 (37.7)	0.38
Elevated LDH, N (%)	13 (29.5)	36 (46.8)	0.04*
With del(17p)/TP53 mutation	9 (20.5)	21 (27.3)	0.59

BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; IGHV, immunoglobulin heavy-chain variable region gene; LDH, lactate dehydrogenase; SD, standard deviation
*Significant at p<0.05

cBTKi discontinuation and subsequent treatments

- Patients in the cBTKi cohort were treated longer with their first cBTKi-based regimen before discontinuation and had longer time from CLL/SLL diagnosis to cBTKi-based regimen initiation than those in the BCL2i cohort (**Table 2**)
- The most common reason for cBTKi-based regimen discontinuation was intolerance (80.2%; n=97)

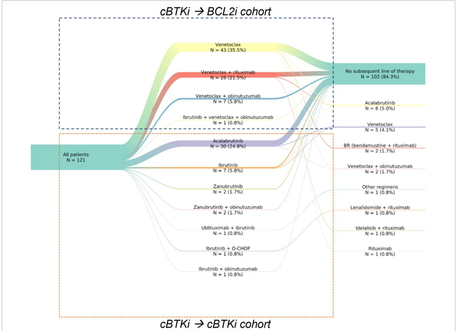
Table 2. Treatment characteristics for the cBTKi and BCL2i cohorts

Treatment characteristics	cBTKi N = 44	BCL2i N = 77	p-value
Time from CLL/SLL diagnosis to cBTKi or BCL2i initiation (months), Mean± SD [Median]	98.4 ± 54.6 [91.0]	76.4 ± 66.7 [62.6]	0.07
Time from first cBTKi discontinuation to cBTKi/BCL2i initiation (months), Mean± SD [Median]	7.3 ± 11.0 [0.51]	7.5 ± 11.7 [1.64]	0.94
Time to first cBTKi discontinuation (months), Mean± SD [Median]	22.8 ± 19.8 [19.6]	14.3 ± 17.1 [10.8]	0.01*
Duration of follow-up (months), Mean± SD [Median]	16.1 ± 11.7 [11.6]	20.1 ± 14.2 [16.4]	0.13
Reasons for cBTKi discontinuation			
Intolerance	35 (79.5%)	62 (80.5%)	-
Patient request	2 (4.5%)	3 (3.9%)	-
Watchful waiting due to low or no disease activity	1 (2.3%)	5 (6.5%)	-
Disease transformation (diffuse large B-Cell or Hodgkin lymphoma)	1 (2.3%)	0 (0.0%)	-
Economic reasons	0 (0.0%)	2 (2.6%)	-
Other	7 (15.9%)	7 (9.1%)	-
Number of prior lines, Mean± SD [Median]	1.7 ± 1.0 [1.0]	1.7 ± 0.8 [2.0]	0.98
Number of prior lines, N (%)			0.44
1	25 (56.8)	37 (48.1)	
2	11 (25.0)	28 (36.4)	
3+	8 (18.2)	12 (15.6)	

BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic lymphoma; SD, standard deviation; SLL, small lymphocytic lymphoma
*Significant at p<0.05

- Most common treatments following the cBTKi-based regimen discontinuation included acalabrutinib (25.2%) and ibrutinib (5.9%) in the cBTKi cohort; and venetoclax (36.1%) and venetoclax+rituximab (21.8%) in the BCL2i cohort (**Figure 1**)

Figure 1. Treatments following cBTKi-based regimen discontinuation[1-3]



BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton tyrosine kinase inhibitor; [1]The most common first cBTKi-based regimens received by patients were ibrutinib-based (118/121 [97.5%]) and acalabrutinib-based (3/121 [2.5%]) regimens; [2]Among patients who did not initiate a subsequent line of therapy, a greater proportion were from the BCL2i cohort (67/102 [65.7%]) relative to the cBTKi cohort (35/102 [34.3%]); [3]One patient who was treated with both a cBTKi and a BCL2i as part of the same regimen was included in the BCL2i cohort

Overall response (OR)

- Of the 79 patients with recorded response, the BCL2i cohort had significantly greater odds of achieving a response compared to the cBTKi cohort (**Figure 2**)

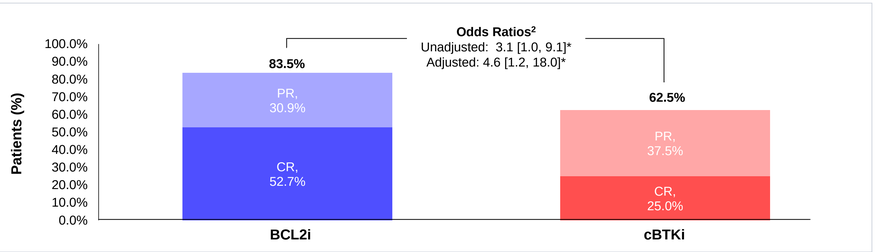
Progression-free survival (PFS)

- The BCL2i cohort had higher PFS KM estimates than cBTKi cohort at 12 months (cBTKi: 79.1%, BCL2i: 87.3%) (**Figure 3**)
- The BCL2i cohort had a 70% lower hazard of progression/death (unadjusted hazard ratio [HR]: 0.6 [confidence interval [CI]: 0.3; 1.5]; adjusted HR: 0.3 [CI: 0.1; 0.8], p=0.023) compared to cBTKi cohort in the Cox PH regression

Time to next treatment or death (TTNT-D)

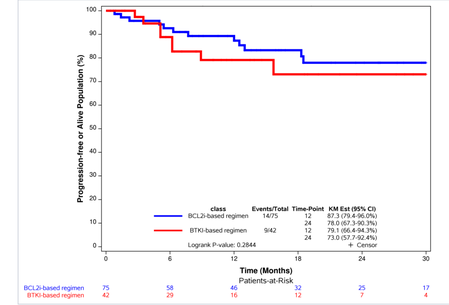
- Relative to cBTKi, the BCL2i cohort had higher, but not statistically significant, TTNT-D KM estimates (12 months: cBTKi: 81.1%, BCL2i: 84.7%), and lower hazards of time to next treatment/death (unadjusted HR: 0.8 [CI: 0.4; 1.9]; adjusted HR: 0.4 [CI: 0.1; 1.0], p=0.055) (**Figure 4**)

Figure 2. Overall response to therapy after the first cBTKi[1]



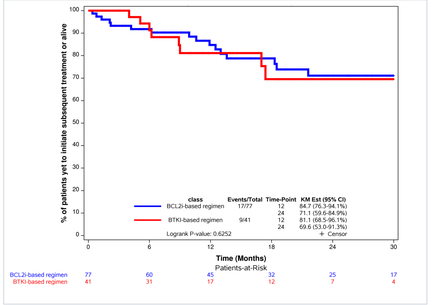
CR, complete remission; PD, progressive disease; PR, partial remission; SD, stable disease
[1]Responses were dichotomized into responder (CR [BCL2i: 52.7%; cBTKi: 25.0%] + PR [BCL2i: 30.9%; cBTKi: 37.5%]) and non-responder (SD [BCL2i: 12.7%; cBTKi: 25.0%]+ PD [BCL2i: 3.6%; cBTKi: 12.5%])
[2]Overall response was compared between cohorts using a logistic regression model, adjusting for age at initiation, sex, time from CLL/SLL diagnosis to initiation, duration of discontinued cBTKi therapy, ECOG, and LDH status
*Significant at p<0.05

Figure 3. PFS for cBTKi vs BTCL2i cohorts[1-2]



BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton tyrosine kinase inhibitor; KM, Kaplan Meier; PFS, progression-free survival; RMST, restricted mean survival time
[1]The estimated RMST at Tau = 39.7 months was 33.1 months (standard error = 2.7) for the BCL2i cohort and 31.1 months (standard error = 1.7) for the cBTKi cohort.
[2]Curves are limited to the time point with at least 10% of the starting population at-risk in both groups.

Figure 4. TTNT-D for cBTKi vs BCL2i cohorts[1-2]



BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton tyrosine kinase inhibitor; KM, Kaplan Meier; RMST, restricted mean survival time; TTNT-D, time to next treatment or death
[1]The estimated RMST at Tau = 43.3 months was 33.6 months (standard error = 2.0) for the BCL2i cohort and 33.4 months (standard error = 3.0) for the cBTKi cohort.
[2]Curves are limited to the time point with at least 10% of the starting population at-risk in both groups.

LIMITATIONS

- As this was a retrospective chart review across multiple centers, there may be differences in clinical data interpretation and possibility of data entry errors
- Findings should be interpreted with care given the limited durations of follow-up, especially in the cBTKi cohort

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