Updated Efficacy and Safety of the Bruton Tyrosine Kinase Degrader BGB-16673 in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Results From the Ongoing Phase 1 CaDAnCe-101 Study

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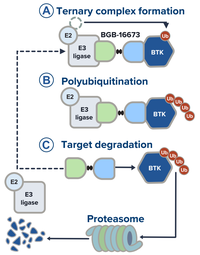
CONCLUSIONS

- In phase 1 of CaDAnCe-101, the novel BTK degrader BGB-16673 was safe and well tolerated in this heavily pretreated population of patients with R/R CLL/SLL
  - Only 2 patients discontinued treatment due to a treatment-related TEAE
  - No treatment-related deaths occurred
  - The 200-mg dose was selected as the recommended dose for expansion for phase 2
- Significant antitumor activity was observed, including in patients with BTK mutations and those previously exposed to cBTK, ncBTK, and BCL2 inhibitors
  - The ORR was 84.8%, and the CR/CRi rate was 4.5%; in the 200-mg dose group, the ORR was 93.8%
  - The ORR in triple-exposed patients was 75.0%
  - Median time to first response was 2.8 months
  - 65.2% of patients remained on treatment with a median follow-up of 15.6 months
- BGB-16673 is being evaluated in ongoing phase 2 and 3 studies in R/R CLL

INTRODUCTION

- Many patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) experience disease progression with Bruton tyrosine kinase (BTK) inhibitors, which can be caused by resistance mutations in BTK[1-3]
- BGB-16673 is an orally available protein degrader that blocks BTK signaling by tagging BTK for degradation through the cell's proteasome pathway, leading to tumor regression (**Figure 1**)[4]
- In preclinical models, BGB-16673 showed central nervous system (CNS) penetration and degraded both wild-type and mutant BTK resistant to covalent BTK (cBTK) (C481S, C481F, C481Y, L528W, T474I) and noncovalent BTK (ncBTK) inhibitors (V416L, M437R, T474I, L528W)[4,5]
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue[6]
- Here, updated safety and efficacy results in patients with relapsed or refractory (R/R) CLL/SLL in phase 1 of CaDAnCe-101 are presented

Figure 1. BGB-16673: a BTK-Targeted CDAC

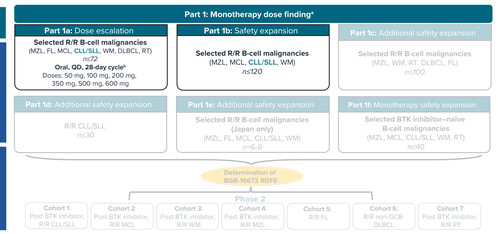


Abbreviations: BTK, Bruton tyrosine kinase; CDAC, chimeric degradation activating compound; ub, ubiquitin.

METHODS

- CaDAnCe-101 (BGB-16673-101; NCT05006716) is a phase 1/2, open-label, dose-escalation and dose-expansion study evaluating BGB-16673 in patients with R/R B-cell malignancies (**Figure 2**)

Figure 2. CaDAnCe-101 Study Design



[a]Data from gray portions of the figure are not included in this presentation. [b]Treatment was administered until progression, intolerance, or other criteria were met for treatment discontinuation. [c]Safety was assessed according to NCI-CTCAE v5.0 in all patients and iwCLL hematologic toxicity criteria in patients with CLL. [d]Response was assessed per iwCLL 2018 criteria after 12 weeks in patients with CLL.

Abbreviations: cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GCB, germinal center B cell; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; R/R, relapsed/refractory; RDFE, recommended dose for expansion; RP2D, recommended phase 2 dose; RT, Richter transformation; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

RESULTS

- As of March 3, 2025, 66 patients with R/R CLL/SLL had received BGB-16673
- Patients were heavily pretreated, with a median of 4 (range, 2-10) prior lines of therapy, and many had high-risk CLL features at study entry (**Table 1**)

Table 1. Baseline Patient Characteristics

Characteristics	Total (N=66)
Age, median (range), years	70 (47-91)
Male, n (%)	45 (68.2)
ECOG PS, n (%)	
0	38 (57.6)
1	27 (40.9)
2	1 (1.5)
CLL/SLL risk characteristics at study entry, n/N with known status (%)	
Binet stage C	29/62 (46.8)
Unmutated IGHV	38/49 (77.6)
del(17p) and/or *TP53* mutation	43/66 (65.2)
Complex karyotype (≥3 abnormalities)	22/44 (50.0)
Mutation status, n/N (%)	
BTK mutation present	24/63 (38.1)
PLCG2 mutation present	10/63 (15.9)
BTK and *PLCG2* mutation present	5/63 (7.9)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	47 (71.2)
cBTK inhibitor	62 (93.9)
ncBTK inhibitor	14 (21.2)
BCL2 inhibitor	54 (81.8)
cBTK + BCL2 inhibitors	42 (63.6)
cBTK + ncBTK + BCL2 inhibitors	12 (18.2)
Discontinued prior BTK inhibitor due to PD, n/N (%)[a]	55/62 (88.7)

[a]The remaining 7 patients discontinued prior BTK inhibitor due to toxicity (n=4), treatment completion (n=2), and other (n=1).
Abbreviations: BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; ncBTK, noncovalent Bruton tyrosine kinase; PD, progressive disease; SLL, small lymphocytic lymphoma.

Safety

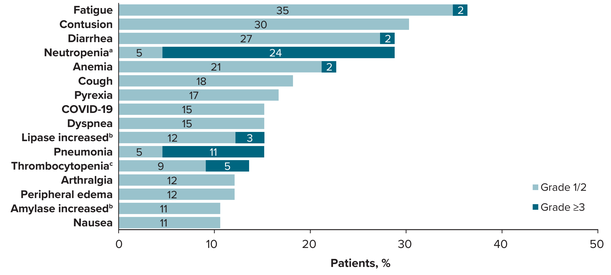
- Overall, BGB-16673 was generally well tolerated (**Table 2**), with fatigue (37%) and contusion (bruising; 30%) among the most common treatment-emergent adverse events (TEAEs; **Figure 3**)
- One patient each had grade 1 and grade 2 atrial fibrillation in the context of infection and progressive disease, respectively
- No pancreatitis occurred
- Major hemorrhages (TEAEs of bleeding that were grade ≥3, serious, or involved the CNS) occurred in 2 patients: grade 1 subarachnoid hemorrhage (n=1) and grade 3 subdural hemorrhage (n=1)
- TEAEs led to death in 4 patients; none were treatment related

Table 2. Overall Safety Summary

Patients, n (%)	Total (N=66)
Any TEAE	63 (95.5)
Any treatment-related	49 (74.2)
Grade ≥3	40 (60.6)
Treatment-related grade ≥3	20 (30.3)
Serious	30 (45.5)
Treatment-related serious	8 (12.1)
Leading to death	4 (6.1)
Treatment-related leading to death	0
Leading to treatment discontinuation	9 (13.6)
Treatment-related leading to treatment discontinuation	2 (3.0)

Median follow-up in safety-evaluable patients: 15.6 months (range, 0.3-30.6+ months).
Abbreviation: TEAE, treatment-emergent adverse event.

Figure 3. Summary of All-Grade TEAEs in ≥10% of All Patients



[a]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [b]All events were laboratory findings and were transient, mostly occurring during the first 1-3 cycles of treatment, with no clinical pancreatitis. [c]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.
Abbreviation: TEAE, treatment-emergent adverse event.

Antitumor Activity

- In 66 response-evaluable patients, the overall response rate (ORR) was 84.8%; in the 200-mg cohort, the ORR was 93.8% (**Table 3**)
  - The complete response (CR)/CR with incomplete marrow recovery (CRi) rate was 4.5%
  - Median time to first response was 2.8 months
- High ORRs were observed in various high-risk patient subgroups (**Table 4**)
  - Responses were observed regardless of specific mutations in key signaling molecules (eg, *TP53*, *BTK*, and *PLCG2)* and in those previously exposed to cBTK, ncBTK and BCL2 inhibitors
- Rapid and significant cytopenia improvement was observed in patients with a response to treatment (**Figure 4**)
- The progression-free survival rate at 12 months was 77.4% (**Figure 5**)

Table 3. Overall Response Rate

	50 mg (n=1)	100 mg (n=22)	200 mg (n=16)	350 mg (n=15)	500 mg (n=12)	Total (N=66)
Best overall response, n (%)						
CR/CRi	0	1 (4.5)	1 (6.3)	0	1 (8.3)	3 (4.5)
PR[a]	1 (100)	11 (50.0)	12 (75.0)	11 (73.3)	9 (75.0)	44 (66.7)
PR-L	0	6 (27.3)	2 (12.5)	0	1 (8.3)	9 (13.6)
SD	0	4 (18.2)	0	0	1 (8.3)	5 (7.6)
PD	0	0	1 (6.3)	1 (6.7)	0	2 (3.0)
Discontinued prior to first assessment	0	0	0	3 (20.0)	0	3 (4.5)
ORR, n (%)[b]	1 (100)	18 (81.8)	15 (93.8)	11 (73.3)	11 (91.7)	56 (84.8)
Time to first response, median (range), months[c]	2.9 (2.9-2.9)	2.8 (2.0-6.2)	2.9 (2.6-8.3)	2.8 (2.6-19.4)	2.8 (2.6-13.8)	2.8 (2.0-19.4)
Time to best response, median (range), months	2.9 (2.9-2.9)	2.8 (2.8-11.1)	3.4 (2.6-13.8)	5.6 (2.6-19.4)	8.3 (2.7-13.8)	3.4 (2.0-19.4)
Duration of exposure, median (range), months	29.6 (29.6-29.6)	7.1 (3.7-23.7)	16.2 (2.9-24.6)	15.6 (0.2-22.8)	15.3 (6.8-21.4)	12.9 (0.2-29.6)

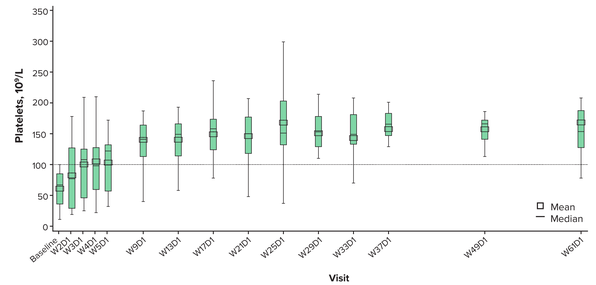
[a]Of 44 patients with PRs, 12 achieved all nodes normalized. [b]Includes best overall response of PR-L or better. [c]In patients with a best overall response of PR-L or better.
Abbreviations: CR, complete response; CRi, complete response with incomplete marrow recovery; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytes; SD, stable disease.

Table 4. High Overall Response Rate in High-Risk Subgroups

Characteristic, n/N with known status (%)	ORR
Double exposure (previously received cBTKi + BCL2i)	38/42 (90.5)
Triple exposure (previously received cBTKi + ncBTKi + BCL2i)	9/12 (75.0)
del(17p) and/or *TP53* mutation	35/43 (81.4)
Complex karyotype (≥3 abnormalities)	16/22 (72.7)
***BTK* mutation**	18/24 (75.0)
***PLCG2* mutation**	9/10 (90.0)

Abbreviations: BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton tyrosine kinase inhibitor; ncBTKi, noncovalent Bruton tyrosine kinase inhibitor; ORR, overall response rate.

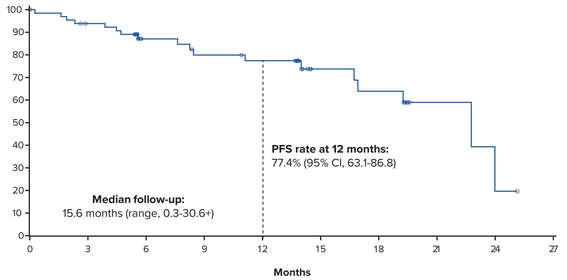
Figure 4. Platelet Count in Patients Who Had Baseline Thrombocytopenia and Responded to Treatment



No. of patients	21	21	21	20	19	21	21	20	21	21	18	14	10	9	8

Abbreviations: D, day; W, week.

Figure 5. Progression-Free Survival



No. at risk:	66	59	37	33	31	15	13	3	1	0

Abbreviation: PFS, progression-free survival.

Study Status

- Enrollment for CaDAnCe-101 phases 1 and 2 is ongoing at >100 study sites across the US, Canada, the UK, France, Georgia, Germany, Italy, Moldova, Spain, Sweden, Turkey, Australia, South Korea, Brazil, and Japan

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DISCLOSURES

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