Updated Efficacy and Safety Results of the Bruton Tyrosine Kinase Degrader BGB-16673 in Patients With Relapsed/Refractory Waldenström Macroglobulinemia From the Ongoing Phase 1 CaDAnCe-101 Study

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CaDAnCe-101

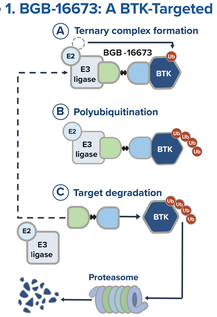
CONCLUSIONS

- In phase 1 of CaDAnCe-101, the BTK degrader BGB-16673 was well tolerated in heavily pretreated patients with R/R WM
  - Only five patients discontinued treatment due to TEAEs
- Promising efficacy was observed, including in patients with BTK resistance mutations, *TP53* and *CXCR4* mutations, and those previously exposed to chemotherapy, proteasome inhibitors, cBTK inhibitors (including more than one), ncBTK inhibitors, and 4 or more prior lines of therapy
  - The ORR was 85.7% (36/42), MRR was 78.6% (33/42), and VGPR was 28.6% (12/42)
  - An ORR of 82.9% (29/35) was observed in patients with high-risk WM, including those with progression on prior BTK inhibitor therapy
  - A rapid improvement in cytopenia was seen in responding patients
  - Two thirds of patients remain on treatment, with only six events in the first 12 months
  - The observed PFS rate at 12 months was 78.3%
- Based on the totality of data available, BGB-16673 is being evaluated in an ongoing phase 2 study in R/R WM

INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors are effective in Waldenström macroglobulinemia (WM) but are associated with toxicities and/or resistance development[1,2]
- 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[3] (**Figure 1**)
- By degrading BTK, BGB-16673 disrupts both inherent BTK catalytic activity and its separate protein scaffolding functions, in contrast to small molecule BTK inhibitors that temporarily block BTK catalytic activity alone[4,5]
- The elimination of BTK by degradation may be effective against treatment-resistant BTK mutants that have been shown to limit the efficacy of current BTK inhibitors[4]
- In preclinical models, BGB-16673 degraded both wild-type BTK and mutant forms of BTK that have shown resistance to covalent and noncovalent BTK inhibitors; additionally, BGB-16673 showed central nervous system (CNS) penetration[3,6]
- In a clinical study, BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue[7]
- Here, updated safety and efficacy results in patients with relapsed/refractory (R/R) WM in phase 1 of CaDAnCe-101 are presented

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

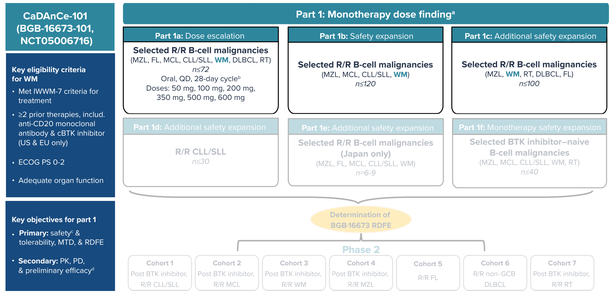


Abbreviations: BTK, Bruton tyrosine kinase; CDAC, chimeric degradation activating compound; ub, ubiquitin.

METHODS

- CaDAnCe-101 (BGB-16673-101; NCT05006716) is a phase 1/2, open-label, dose-escalation, and dose-expansion study evaluating BGB-16673 in adults 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. [d]Responses were assessed per modified IWWM-6 criteria after 12 weeks.[2]
Abbreviations: BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GCB, germinal center B cell; IWWM, International Workshop on Waldenström Macroglobulinemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; RDFE, recommended dose for expansion; R/R, relapsed/refractory; RT, Richter transformation; WM, Waldenström macroglobulinemia.

RESULTS

- As of August 22, 2025, 42 patients with WM had received BGB-16673
- Patients were heavily pretreated, with a median of 3 prior lines of therapy (range, 2-11) (**Table 1**)
- The median study follow-up was 11.7 months (range, 0.8-33.5+ months)

Table 1. Baseline Patient Characteristics

	Total (N=42)
Age, median (range), years	72 (46-81)
Male, n (%)	27 (64.3)
ECOG PS, n (%)	
0	19 (45.2)
1	21 (50.0)
2	2 (4.8)
Hemoglobin, median (range), g/L	103.0 (60.0-146.0)
Hemoglobin ≤110 g/L, n (%)	29 (69.0)
Neutrophils, median (range), 10^9/L	2.8 (0.2-7.4)
Neutrophils ≤1.5×10^9/L, n (%)	12 (28.6)
Platelets, median (range), 10^9/L	153.5 (14.0-455.0)
Platelets ≤100×10^9/L, n (%)	8 (19.0)
IgM, median (range), g/L	33.2 (0.3-92.6)
Mutation status, n (%)[a]	
MYD88 mutation	34 (81.0)
CXCR4 mutation	19 (45.2)
BTK mutation	13 (31.0)
TP53 mutation	23 (54.8)
PLCG2 mutation	3 (7.1)
No. of prior lines of therapy, median (range)	3 (2-11)
Prior therapy, n (%)	
cBTK inhibitor	42 (100)
Anti-CD20 antibody	42 (100)
Chemotherapy	39 (92.9)
Proteasome inhibitor	13 (31.0)
BCL2 inhibitor	10 (23.8)
ncBTK inhibitor[b]	7 (16.7)
Discontinued prior BTK inhibitor due to PD, n (%)	35 (83.3)

Data cutoff: August 22, 2025.
[a]Confirmed by central laboratory. [b]All seven patients with ncBTK inhibitor exposure were also exposed to a cBTK inhibitor.
Abbreviations: BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; IgM, immunoglobulin M; ncBTK, noncovalent Bruton tyrosine kinase; PD, progressive disease.

Safety

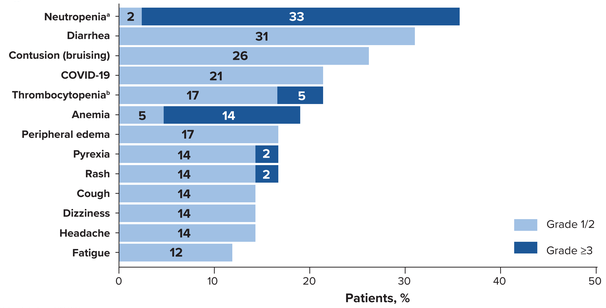
- The overall safety summary is shown in **Table 2**
- The most common treatment-emergent adverse events (TEAEs) were neutropenia (35.7%) and diarrhea (31.0%) (**Figure 3**)
- Eight patients (19.0%) had a grade ≥3 infection
- Major hemorrhage, defined as grade ≥3, serious, or any CNS bleeding, occurred in one patient; this was caused by concurrent gastritis/duodenitis and was unrelated to treatment
- Febrile neutropenia occurred in one patient
- Five patients had a TEAE that led to treatment discontinuation
- Three patients had a TEAE (cerebral aspergillosis, n=2; septic shock in the context of PD, n=1) that led to death

Table 2. TEAE Summary

Patients, n (%)	Total (N=42)
Any TEAE	41 (97.6)
Any treatment-related	33 (78.6)
Grade ≥3	26 (61.9)
Treatment-related grade ≥3	18 (42.9)
Serious	16 (38.1)
Treatment-related serious	6 (14.3)
Leading to death[a]	3 (7.1)
Treatment-related leading to death	2 (4.8)
Leading to treatment discontinuation	5 (11.9)

Data cutoff: August 22, 2025. Median follow-up: 11.7 months (range, 0.8-33.5+ months).
[a]Cerebral aspergillosis, n=2; septic shock (200-mg dose level), in the context of PD, n=1.
Abbreviations: PD, progressive disease; TEAE, treatment-emergent adverse event.

Figure 3. TEAEs in ≥10% of All Patients



Data cut off: August 22, 2025.
[a]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [b]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.
Abbreviation: TEAE, treatment-emergent adverse event.

Efficacy

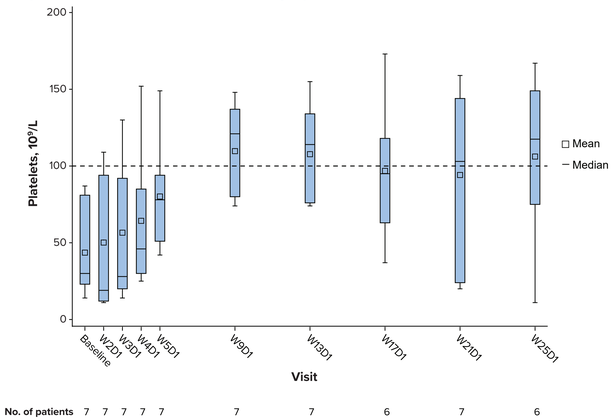
- The overall response rate (ORR) was 85.7% (36/42) (**Table 3**)
- Responses were observed at all dose levels and in patients with ≥4 prior lines of therapy (16/19 [84.2%]) and with ≥2 prior BTK inhibitors (16/17 [94.1%])
  - These included patients previously treated with chemotherapy (33/39), proteasome inhibitors (11/13), or noncovalent BTK inhibitors (7/7), and those with progression on prior BTK inhibitor therapy (29/35)
  - Responses were seen regardless of specific baseline mutation status, including in those with or without *MYD88*, *TP53* and *CXCR4* mutations
- In patients who had a response, rapid and significant cytopenia improvement was observed (**Figure 4**)
  - Hemoglobin improved from 97.5 g/L at baseline to 114 g/L at week 9 (n=24)
  - Neutrophil count improved from 0.92×10^9/L at baseline to 1.68×10^9/L at week 13 (n=10)
- Among the 36 patients who had a response, 15 maintained a response for ≥12 months; among the rest, 15 were censored and six experienced events before 12 months
- The 12-month progression-free survival (PFS) rate was 78.3% (95% CI, 60.8-88.6) (**Figure 5**)
- Twenty-eight patients remained on treatment; progressive disease was the most common reason for treatment discontinuation (14.3%)

Table 3. Summary of Disease Responses in All Patients and by Mutation Status

	Total (N=42)[a]
Best overall response, n (%)	
VGPR	12 (28.6)
PR	21 (50.0)
MR	3 (7.1)
SD	4 (9.5)
PD	1 (2.4)
Discontinued prior to first assessment	1 (2.4)
ORR, n (%)[b]	36 (85.7)
MRR, n (%)[c]	33 (78.6)
Time to first response, median (range), months[d]	1.0 (0.9-6.5)
Time to best overall response, median (range), months[d]	2.4 (0.9-7.4)
Mutation status, n/N tested (%)	**ORR (N=42)[a]**
BTK	
Mutated	13/13 (100)
Unmutated	23/29 (79.3)
MYD88	
Mutated	29/34 (85.3)
Unmutated	7/8 (87.5)
CXCR4	
Mutated	18/19 (94.7)
Unmutated	18/23 (78.3)
TP53	
Mutated	20/23 (87.0)
Unmutated	16/19 (84.2)
PLCG2	
Mutated	2/3 (66.7)
Unmutated	34/39 (87.2)

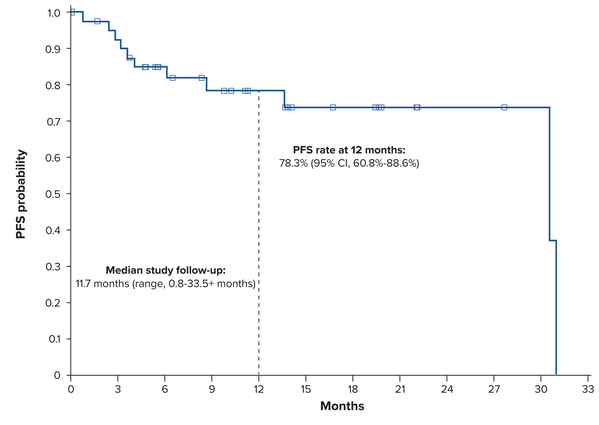
[a]Efficacy-evaluable population. [b]Includes best overall response of MR or better. [c]Includes best overall response of PR or VGPR. [d]In patients with a best overall response of MR or better.
Abbreviations: MRR, major response rate; MR, minor response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Figure 4. Rapid and Significant Platelet Improvement in Patients With Disease Response Who Had Baseline Thrombocytopenia



Abbreviations: D, day; W, week.

Figure 5. Progression-Free Survival



Abbreviation: PFS, progression-free survival.

Study Status

- Enrollment for CaDAnCe-101 phase 1 and phase 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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