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

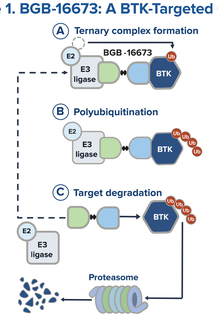
CONCLUSIONS

- 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

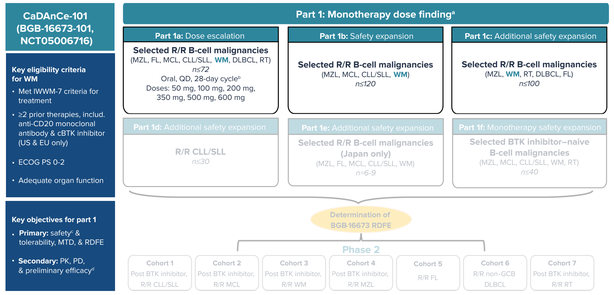


Abbreviations: BTK, Bruton tyrosine kinase; CDAC, chimeric degradation activating compound; ub, ubiquitin.

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 4 weeks.[8]
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.
[b]Confirmed by central laboratory. [a]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

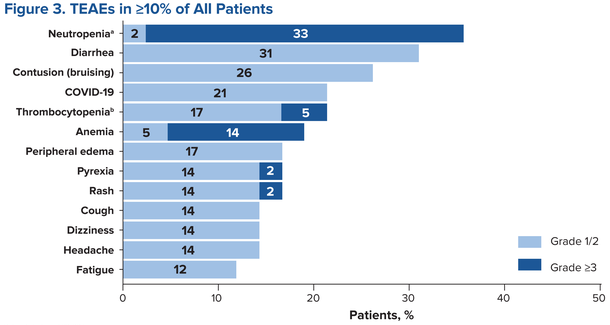
- The overall safety summary is shown in **Table 2**
- The most common treatment-emergent adverse events (TEAEs) were neutropenia (35.7%) and diarrhea (31.0%) (**Figure 3**)
- Eight patients (19.0%) had a grade ≥3 infection
- Major hemorrhage, defined as grade ≥3, serious, or any CNS bleeding, occurred 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

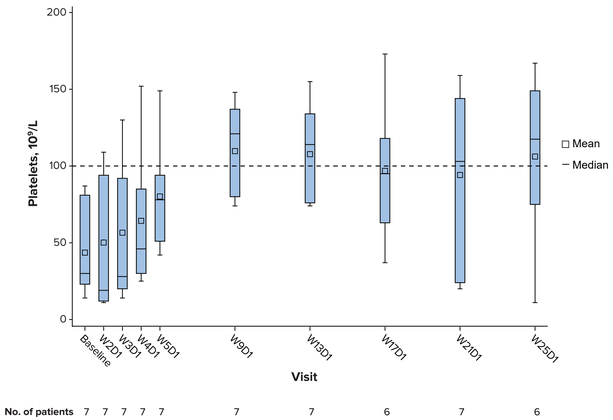
- The overall response rate (ORR) was 85.7% (36/42) (**Table 3**)
- Responses were observed at all dose levels and in patients with ≥4 prior lines of therapy (16/19 [84.2%]) and with ≥2 prior BTK inhibitors (16/17 [94.1%])
  - These included patients previously treated with chemotherapy (33/39), proteasome 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)

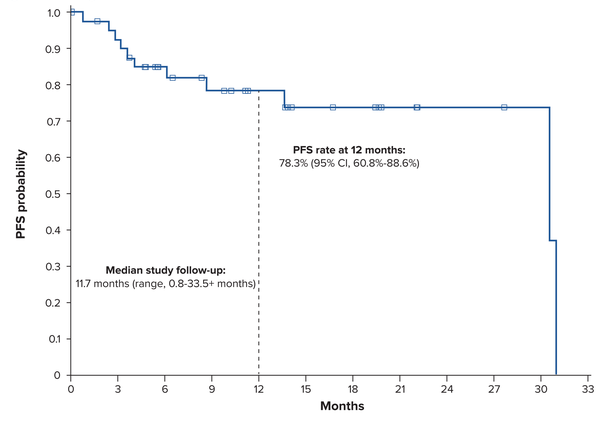
[a]Efficacy-evaluable population. [b]Includes best overall response of MR or better. [c]Includes best overall response of PR or VGPR. [d]In patients with a best overall response of MR or better.
Abbreviations: MRR, major response rate; MR, minor response; ORR, overall response rate; PD, progressive disease;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

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeOne Medicines, Ltd. Medical writing was provided by Sonam Mehrotra, PhD of Nucleus Global, an Inizio company, and supported by BeOne Medicines.

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Presented at the 67th ASH Annual Meeting and Exposition; December 6-9, 2025; Orlando, FL