BGB-16673, a Bruton Tyrosine Kinase Degrader, in Patients With Relapsed/Refractory Waldenström Macroglobulinemia: a Phase 1 CaDAnCe-101 Study Update

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CaDAnCe-101

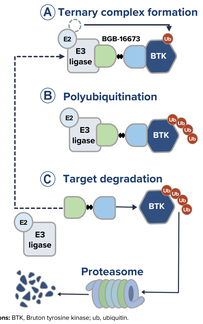
CONCLUSIONS

- The novel BTK degrader BGB-16673 continues to demonstrate a favorable safety profile and high efficacy in heavily pretreated patients with R/R WM
- As of the data cutoff, 53.5% of patients remained on treatment
- No new safety signals were observed at a median duration of exposure of 14.6 months
- Promising antitumor activity was observed, regardless of high-risk features
  - The ORR was 83.7% (36/43), the MRR was 76.7% (33/43), and the VGPR was 30.2% (13/43)
  - High ORR was observed regardless of mutations in *CXCR4* (100%), *TP53* (91.3%), *BTK* (100%), and *PLCG2* (100%)
  - A rapid improvement in cytopenia was seen in responding patients
  - PFS was sustained, with an estimated 18-month PFS rate of 68.6%
- The phase 2 portion of the CaDAnCe-101 study in WM is actively enrolling

INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors are effective for the treatment of Waldenström macroglobulinemia (WM); however, treatment resistance and intolerance can emerge[1,2]
- BGB-16673 is a potential first-in-class oral BTK degrader that tags BTK for degradation through the cell's proteasome pathway, leading to tumor regression[3] (**Figure 1**)
  - Degrades wild-type BTK and many BTK mutations associated with resistance to covalent and noncovalent BTK inhibitors with the broadest activity among BTK-targeting agents[3,4]
  - Disrupts BTK kinase activity and its ability to transduce signals through its scaffolding function, in contrast to BTK inhibitors which only block kinase activity[5,6]
  - A single BGB-16673 molecule can degrade multiple BTK proteins[6]
  - Demonstrates central nervous system penetration in preclinical models[7]
  - Drives robust clinical responses across several B-cell malignancies[8]
- Here we report updated safety and efficacy results of BGB-16673 in patients with relapsed/refractory (R/R) WM in the phase 1 portion of the CaDAnCe-101 study

Figure 1. BGB-16673: the Broadest Activity Among BTK-Targeting Agents

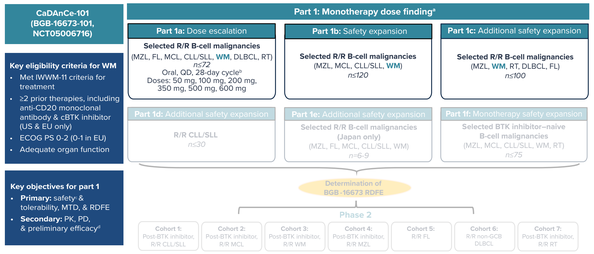


Abbreviations: BTK, Bruton tyrosine kinase; ub, ubiquitin.

METHODS

- CaDAnCe-101 (BGB-16673-101; NCT05006716) is an ongoing open-label, phase 1/2 trial (**Figure 2**)
  - BGB-16673 was orally administered once daily to eligible patients with R/R WM
- The primary objectives were to determine the safety/tolerability (NCI-CTCAE v5.0), maximum tolerated dose, and recommended dose for expansion of BGB-16673
- A key secondary objective was to determine the overall response rate (ORR, defined as ≥minor response; International Workshop on Waldenström Macroglobulinemia 11 consensus criteria)[9]
  - The major response rate (MRR) was defined as ≥partial response

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-11 criteria after 4 weeks.[9]
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 the February 25, 2026, data cutoff, 43 patients with R/R WM received BGB-16673 (100 mg, n=15; 200 mg, n=15; 350 mg, n=13)
- Median age was 72 (range, 46-81) years, and median number of prior therapies was 3 (range, 2-11); baseline demographics and clinical characteristics are shown (**Table 1**)
- Median study follow-up was 16.6 (range, 0.8-39.7) months

Table 1. Baseline Patient Characteristics

Characteristic	Total (N=43)
Age, median (range), years	72 (46-81)
Male, n (%)	28 (65.1)
ECOG PS, n (%)	
0	20 (46.5)
1	21 (48.8)
2	2 (4.7)
Hemoglobin, median (range), g/L	103.0 (60.0-146.0)
Hemoglobin <110 g/L, n (%)	30 (69.8)
Neutrophils, median (range), 10^9/L	2.7 (0.2-7.4)
Neutrophils <1.5×10^9/L, n (%)	12 (27.9)
Platelets, median (range), 10^9/L	152.0 (14.0-455.0)
Platelets <100×10^9/L, n (%)	9 (20.9)
IgM, median (range), g/L	33.6 (0.3-92.6)
Mutation status at study entry, n/N with known status (%)[a]	
MYD88 mutated	33/42 (78.6)
CXCR4 mutated	19/42 (45.2)
TP53 mutated	23/42 (54.8)
BTK mutated	13/42 (31.0)
PLCG2 mutated	3/42 (7.1)
No. of prior lines of therapy, median (range)	3 (2-11)
Prior therapy, n (%)	
Chemotherapy	40 (93.0)
Anti-CD20 monoclonal antibodies	43 (100)
cBTK inhibitors	43 (100)
ncBTK inhibitors	7 (16.3)
BCL2 inhibitors	10 (23.3)
Proteasome inhibitors	14 (32.6)
Discontinued prior BTK inhibitor due to PD, n (%)	36 (83.7)

[a]Mutation status was unknown in 1 patient.
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

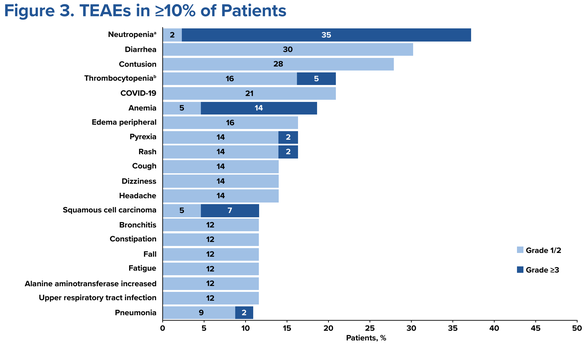
- The overall safety summary is shown in **Table 2**
- The most common any-grade treatment-emergent adverse events (TEAEs) were neutropenia/neutrophil count decreased in 16 patients (37.2%), diarrhea in 13 patients (30.2%), and contusion (bruising) in 12 patients (27.9%) (**Figure 3**)
- The most common grade ≥3 TEAEs included neutropenia/neutrophil count decreased in 15 patients (34.9%) and anemia in six patients (14.0%)
  - Febrile neutropenia occurred in one patient
  - No atrial fibrillation occurred
  - Major hemorrhage (grade 3 hematemesis caused by concurrent gastritis/duodenitis) occurred in one patient (2.3%)
  - Grade ≥3 infections were reported in 9 patients (20.9%)
- Seven patients (16.3%) had TEAEs that led to treatment discontinuation
- Three patients (7.0%) had a TEAE that led to death, including two patients from cerebral aspergillosis (one patient received a steroid within the 30 days prior to the event and had other risk factors, including neutropenia and hypogammaglobulinemia; the other patient had multiple co-morbidities and hypogammaglobulinemia) and one from septic shock in the context of progressive disease
  - There were no new patient deaths due to TEAEs since the last data cutoff (August 22, 2025)

Table 2. Overall Safety Summary

Patients, n (%)	Total (N=43)
Any TEAE	42 (97.7)
Any treatment-related	35 (81.4)
Grade ≥3	29 (67.4)
Treatment-related	18 (41.9)
Serious	19 (44.2)
Treatment-related	7 (16.3)
Leading to dose reduction	3 (7.0)
Treatment-related	3 (7.0)
Leading to treatment discontinuation	7 (16.3)
Treatment-related	4 (9.3)
Leading to death	3 (7.0)
Treatment-related	2 (4.7)

Abbreviation: TEAE, treatment-emergent adverse event.

Figure 3. TEAEs in ≥10% of Patients



Median duration of exposure: 14.6 (range, 0.3-38.0) months. The values of any-grade TEAEs have been calculated from individual grade 1/2 and grade ≥3 values rounded to the nearest whole number. [a]Neutropenia combines preferred terms *neutropenia* and *neutrophil count decreased*. [b]Thrombocytopenia combines preferred terms *thrombocytopenia* and *platelet count decreased*.
Abbreviation: TEAE, treatment-emergent adverse event.

Efficacy

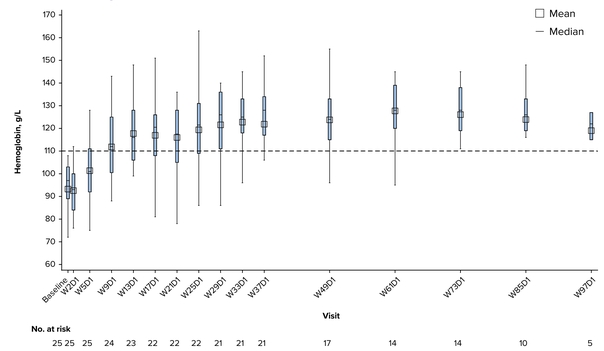
- Among the 43 response-evaluable patients, the ORR was 83.7% (n=36), the MRR was 76.7% (n=33), and the very good partial response (VGPR) rate was 30.2% (n=13); responses were ongoing at data cutoff
- High ORR was observed in patients with high-risk disease features (**Table 3**)
  - The ORR was 80% (n=16/20) in patients with ≥4 prior therapies, 80% (n=24/30) in patients with disease refractory to last BTK inhibitor, and 100% (n=13/13) in patients with disease bearing *BTK* mutations
- High MRR was observed regardless of mutations in *MYD88* (78.8%), *CXCR4* (89.5%), *TP53* (91.3%), *BTK* (100%), and *PLCG2* (100%)
- In patients who had a response, rapid and significant cytopenia improvement was observed (**Figure 4**)
  - Median hemoglobin improved from 97.0 g/L at baseline (n=25) to 112 g/L at week 9 (n=24)
  - Median neutrophil count improved from 0.82×10^9/L (n=10) at baseline to 1.68×10^9/L at week 13 (n=9)
  - Median platelet count improved from 30.5×10^9/L (n=8) at baseline to 123.5×10^9/L at week 9 (n=8)
- Responses deepened over time as evidenced by difference between first overall response at a median of 1.0 (range, 0.9-8.2) months and the best overall response at a median of 2.4 (range, 0.9-12.2) months
  - Among the 36 responders, 20 maintained a response for ≥12 months and 8 patients maintained a response for ≥24 months
- The estimated 18-month progression-free survival (PFS) rate was 68.6% (median PFS follow-up, 19.1 months) (**Figure 5**)
- At the data cutoff, 23 patients (53.5%) remained on treatment; of the 20 patients who discontinued treatment, the primary reason for discontinuation was progressive disease in eight patients (18.6%)

Table 3. ORR by Prior Therapy and Mutation Status

Subgroup	ORR, n/N[a] (%)
Overall	36/43 (83.7)
Number of lines of prior anticancer therapies	
<4	20/23 (87.0)
≥4	16/20 (80.0)
Number of prior BTK inhibitor therapies	
≤1	20/25 (80.0)
≥2	16/18 (88.9)
Refractory to last BTK inhibitor[b]	
Yes	24/30 (80.0)
No	3/3 (100.0)
***MYD88* mutation**	
Yes	29/33 (87.9)
No	7/9 (77.8)
***CXCR4* mutation**	
Yes	19/19 (100.0)
No	17/23 (73.9)
***TP53* mutation**	
Yes	21/23 (91.3)
No	15/19 (78.9)
***BTK* mutation**	
Yes	13/13 (100.0)
No	23/29 (79.3)
***PLCG2* mutation**	
Yes	3/3 (100.0)
No	33/39 (84.6)

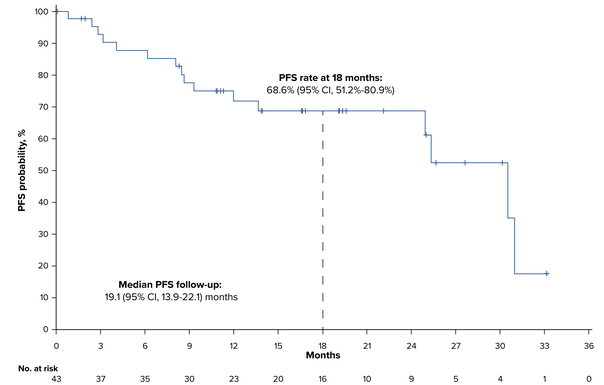
[a]Percentages are calculated based on patients with known status. [b]Defined as having a best overall response of stable disease or less or progressive disease within 7 days of the end of treatment.
Abbreviations: BTK, Bruton tyrosine kinase; ORR, overall response rate.

Figure 4. Rapid and Significant Cytopenia Improvement in Patients With Disease Response Who Had Baseline Anemia



Abbreviations: D, day; W, week.

Figure 5. Progression-Free Survival



Data cutoff: February 25, 2026. Median PFS requires further follow up.
Abbreviation: PFS, progression-free survival.

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DISCLOSURES

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