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

P229

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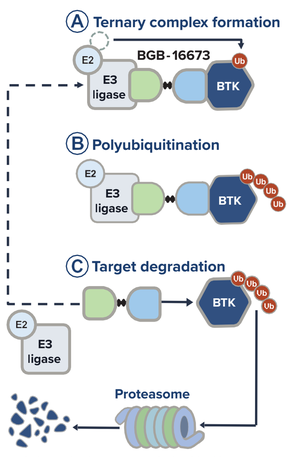
INTRODUCTION

- 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 a potential first-in-class protein degrader that blocks BTK signaling by tagging BTK for degradation through the cell's proteasome pathway[3] (**Figure 1**)
- In preclinical models, BGB-16673 degraded both wild-type and mutant BTK resistant to covalent BTK (cBTK) inhibitors (C481S, C481F, C481Y, L528W, T474I) and noncovalent BTK (ncBTK) inhibitors (V416L, M437R, T474I, L528W), leading to tumor suppression[3,4]
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue[5]
- Here, updated safety and efficacy results are presented in patients with relapsed or refractory (R/R) WM in phase 1 of CaDAnCe-101

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



Attributes and Potential Advantages of BGB-16673

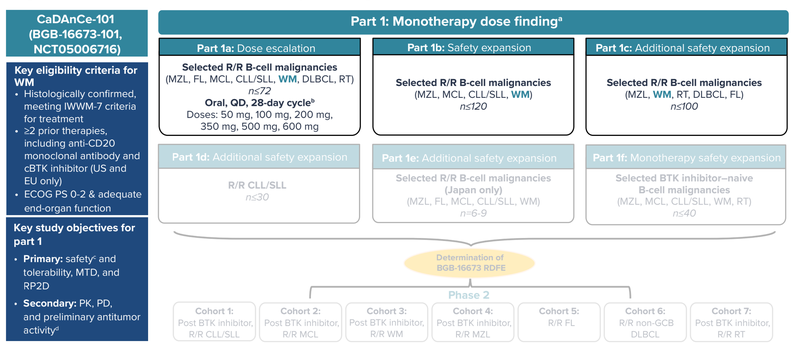
- Catalytic pharmacology that does not require sustained target binding
- Can interrupt formation of oncogenic protein complexes (scaffolding)
- Potential to overcome resistance mutations (eg, BTK C481S, C481F, C481Y, L528W, and V416L)
- Substantially reduced immunomodulatory drug activity; Aiolos and Ikaros are not significantly degraded

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 figure are not included in this presentation. [b] Bayesian optimal interval design with 6 dose levels (50-600 mg orally QD). [c] Safety was assessed according to CTCAE v5.0; DLTs were assessed during the first 4 weeks. [d] Responses were assessed per IWWM-6, modified Owen 2013 criteria after 4 weeks.
cBTK, covalent BTK; GCB, germinal center B-cell; RT, Richter transformation.

RESULTS

Disposition

- As of September 2, 2024, 27 patients with R/R WM enrolled across parts 1a-1c received BGB-16673
- Patients had a median of 3 (range, 2-11) prior lines of therapy; all 4 patients with prior noncovalent BTK inhibitor exposure were subsequently exposed to a covalent BTK inhibitor (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics

	Total (N=27)
Age, median (range), years	73.0 (56-81)
Male, n (%)	15 (55.6)
ECOG PS, n (%)	
0	14 (51.9)
1	12 (44.4)
2	1 (3.7)
Hemoglobin, median (range), g/dL	10.3 (6.0-13.5)
Neutrophils, median (range), 10^9/L	2.7 (0.21-7.43)
Platelets, median (range), 10^9/L	157 (14-455)
Mutation status, n/N with known status (%)[a]	
MYD88 mutation present	24/26 (92.3)
CXCR4 mutation present	12/25 (48.0)
BTK mutation present	11/25 (44.0)
TP53 mutation present	13/25 (52.0)
IgM, median (range), g/L	37.4 (2.8-74.4)
No. of prior lines of therapy, median (range)	3.0 (2-11)
Prior therapy, n (%)	
cBTK inhibitor	27 (100)
Chemotherapy	25 (92.6)
Proteasome inhibitor	9 (33.3)
BCL2 inhibitor	5 (18.5)
ncBTK inhibitor[b]	4 (14.8)
Discontinued prior BTK inhibitor due to PD, n (%)	21 (77.8)

Data cutoff: September 2, 2024.
[a] Confirmed by central laboratory. [b] All 4 patients with ncBTK inhibitor exposure were exposed to a cBTK inhibitor.
cBTK, covalent BTK; IgM, immunoglobulin M; ncBTK, noncovalent BTK.

Safety

- Overall, 92.6% of patients (n=25) experienced all-grade TEAEs and 40.7% (n=11) experienced grade ≥3 TEAEs (**Table 2**)
- No DLTs occurred; maximum tolerated dose (MTD) was not reached with doses up to 350 mg
- Neutropenia was the most frequent all-grade (29.6%) and grade ≥3 (25.9%) TEAE; no events of atrial fibrillation, hypertension, major hemorrhage, febrile neutropenia, or pancreatitis occurred
- TEAEs led to 1 death (septic shock in context of PD) and no treatment discontinuations

Table 2. Overall Safety Summary and TEAEs in ≥10% of All Patients

Patients, n (%)	Total (N=27)
Any TEAE	25 (92.6)
Any treatment-related	19 (70.4)
Grade ≥3	11 (40.7)
Treatment-related	7 (25.9)
Serious	7 (25.9)
Treatment-related	2 (7.4)
Leading to death[a]	1 (3.7)
Treatment-related	0
Leading to treatment discontinuation	0

Patients, n (%)	Total (N=27)	
	All Grade	Grade ≥3
Neutropenia[b]	8 (29.6)	7 (25.9)
Diarrhea	7 (25.9)	0
Anemia	5 (18.5)	3 (11.1)
Contusion (bruising)	5 (18.5)	0
Rash	5 (18.5)	0
Thrombocytopenia[c]	5 (18.5)	2 (7.4)
Amylase increased	4 (14.8)	0
Dizziness	4 (14.8)	0
Pyrexia	4 (14.8)	1 (3.7)
Arthralgia	3 (11.1)	0
Constipation	3 (11.1)	0
COVID-19	3 (11.1)	0
Fall	3 (11.1)	0
Headache	3 (11.1)	0
Lipase increased	3 (11.1)	1 (3.7)
Muscle spasms	3 (11.1)	0
Petechiae	3 (11.1)	0
Upper respiratory tract infection	3 (11.1)	0

[a] Septic shock (200-mg dose level) in the context of PD. [b] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*.
[c] Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

Antitumor Activity

- In 27 efficacy-evaluable patients, ORR was 81.5% (n=22) (**Table 3**)
- Responses were observed starting at the lowest dose (100 mg; 7/9), in patients with prior cBTK inhibitor (22/27) or ncBTK inhibitor (4/4) treatment (**Figure 3**), and regardless of specific mutations
- Rapid IgM decline was seen in all patients at all dose levels; 1 patient had an IgM flare and/or rebound 1 week after starting treatment and went on to develop a PR (**Figure 4**)
- In patients with responses, rapid and significant improvement in cytopenias was observed

Table 3. Overall Response Rates in All Patients and by Mutation Status

	Total (N=27)
Best overall response, n (%)	
VGPR	7 (25.9)
PR	13 (48.1)
MR	2 (7.4)
SD	3 (11.1)
Not evaluable	1 (3.7)
Discontinued prior to first assessment	1 (3.7)
ORR, n (%)[a]	22 (81.5)
Major response rate, n (%)[b]	20 (74.1)
Disease control rate (DCR), n (%)[c]	25 (93.0)
Follow-up, median (range), months	5.0 (0.8-24.6)
Time to first response, median (range), months[e]	1.0 (0.9-3.7)

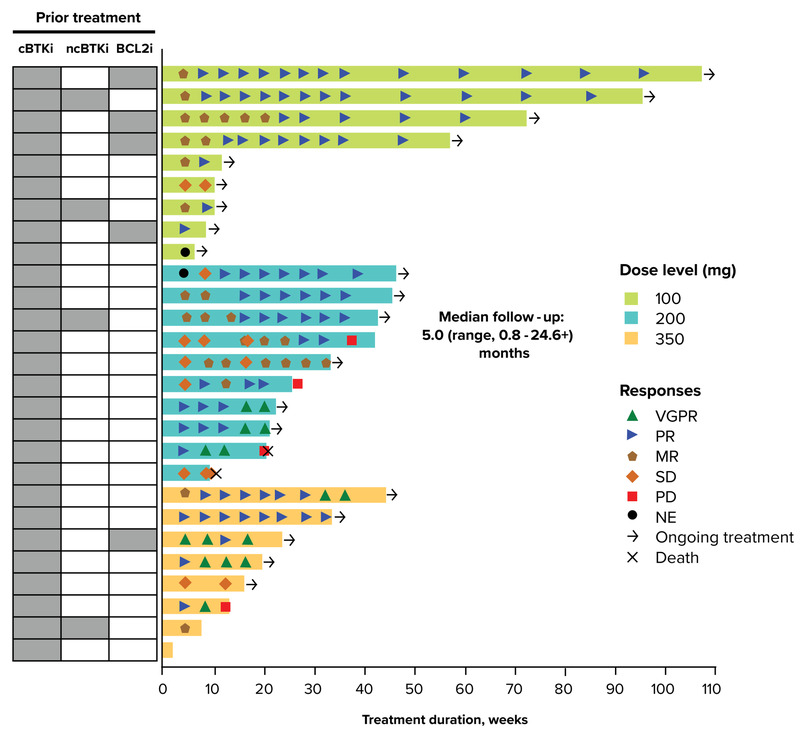
Mutation status, n/N tested (%)	Total (N=27)
BTK	
Mutated	10/11 (90.9)
Unmutated	11/14 (78.6)
Unknown	1/2 (50.0)
MYD88	
Mutated	20/24 (83.3)
Unmutated	1/2 (50.0)
Unknown	1/1 (100)
CXCR4	
Mutated	11/12 (91.7)
Unmutated	10/13 (76.9)
Unknown	1/2 (50.0)
TP53	
Mutated	12/13 (92.3)
Unmutated	9/12 (75.0)
Unknown	1/2 (50.0)

[a] Includes best overall response of MR or better. [b] Includes best overall response of PR or VGPR. [c] Includes best overall response of SD or better. [d] In patients with a best overall response better than SD.
cBTK, covalent BTK; MR, minor response; ncBTK, noncovalent BTK; VGPR, very good partial response.

CONCLUSIONS

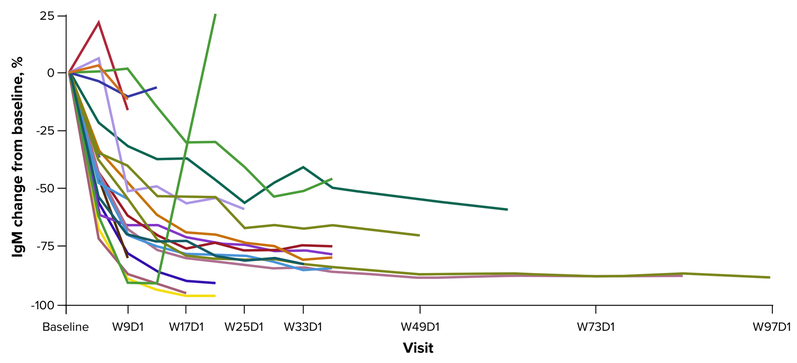
- In phase 1 of CaDAnCe-101, the BTK degrader BGB-16673 was well tolerated in heavily pretreated patients with R/R WM
  - No DLTs occurred; MTD was not reached
  - No atrial fibrillation or hypertension reported
- Very good partial response 25.9% (7/27 patients); ORR 81.5% (22/27); disease control rate 93.0% (25/27)
  - Rapid decline in IgM with median time to first response of 1.0 month
  - Rapid improvement in cytopenias seen in patients who experience disease response
  - Responses continue to deepen over time (median 5.0-month follow-up)
- Promising antitumor activity, including in patients with:
  - BTK inhibitor–resistant mutations
  - *TP53* and *CXCR4* mutations
  - Previous exposure to cBTK inhibitors, ncBTK inhibitors, and BCL2 inhibitors
- These data support further investigation of BGB-16673 clinical activity in patients with WM; enrollment in CaDAnCe-101 continues

Figure 3. Treatment Duration and Response



Data cutoff: September 2, 2024. First disease assessment at 4 weeks.
cBTKi, covalent BTK inhibitor; MR, minor response; ncBTKi, noncovalent BTK inhibitor; NE, not evaluable; VGPR, very good partial response.

Figure 4. Percentage Change From Baseline in IgM



Patient with rapid IgM increase had WM mutations in *BTK*, *MYD88*, *CXCR4*, and *TP53* at baseline, paused treatment for 2-3 weeks due to COVID-19 infection, and developed rapid progression shortly after restarting treatment.
IgM, immunoglobulin M.

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, and Brazil

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DISCLOSURES

DR-W: Consulting or advisory role: AbbVie, AstraZeneca, BeiGene, Janssen-Cilag, Lilly; Travel, accommodations, expenses: AbbVie, BeiGene, Janssen-Cilag. **JFS:** Consultancy: Genor Bio, TG Therapeutics; Honoraria: AbbVie, AstraZeneca, BeiGene, BMS, Gilead, Janssen, Roche; Research funding: AbbVie, BMS, Roche; Speaker's bureau: AbbVie, AstraZeneca, BMS, Roche. **CST:** Honoraria: BeiGene, Janssen, AbbVie, AstraZeneca, Gilead; Research funding: BeiGene, Janssen, AbbVie. **CYC:** Consultant, honoraria, membership on an entity's board of directors or advisory committees: Roche, Janssen, MSD, Gilead, Ascentage Pharma, AstraZeneca, Lilly. **RDP:** Honoraria: Sanofi Aventis, AstraZeneca, MJH Life Sciences, OncLive; Research funding: BMS, GSK. **JNA:** Consulting or advisory role: AbbVie, Adaptive Biotechnologies, ADC Therapeutics, AstraZeneca, BeiGene, Genentech, Janssen, Lilly, Merck, NeoGenomics, Pharmacyclics; Research funding: BeiGene, Celgene/BMS, Genentech; Speaker's bureau: AbbVie, BeiGene. **JT:** Research funding: BeiGene, BMS, Cellectar, Roche. **RA:** Consulting or advisory role: ADCT, Autolus, Genentech, Genmab, Merck, Roche (Chair Steering Committee for SKYGLO Trial); Research funding: BeiGene, Daiichi Sankyo Inc., Gilead, Merck, Millenium Pharmaceuticals, Regeneron, Seattle Genetics, Genentech, Roche, Takeda. **HE:** Consultancy, research funding, honoraria, speakers bureau: AbbVie/Pharmacyclics, BeiGene, Genentech, Incyte, MorphoSys; Research funding: AstraZeneca, Atara, BMS, Gilead/Kite, Juno. **PLZ:** Honoraria and speaker's bureau: Kyowa Kirin, Roche, AbbVie, BeiGene, BMS, Gilead, Novartis, Incyte, Sobi. **ML:** Honoraria: Janssen, AbbVie; Advisory board: Janssen, Sobi, AbbVie, Recordati. **SPT:** Consulting or advisory role: BeiGene, Ono, Janssen, AbbVie/Pharmacyclics; Research funding: BeiGene, Janssen, AbbVie/Pharmacyclics. **KB:** Employment: BeiGene. **SF:** Employment and may own stock: BeiGene; BMS; Advisory role, travel, accommodations, or expenses: BeiGene. **DP:** Employment: BeiGene. **AA:** Employee and equity holder in publicly traded company: BeiGene. **AMF:** Honoraria and Consulting or advisory role: AbbVie, BeiGene, AstraZeneca, Janssen; Travel, accommodations, expenses: AbbVie, BeiGene, AstraZeneca.

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