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

P1119

CaDAnCe-101

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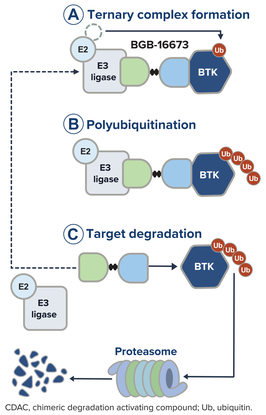
INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors have become the standard of care for treating patients with some B-cell malignancies, including CLL/SLL, Waldenström macroglobulinemia (WM), mantle cell lymphoma, marginal zone lymphoma (MZL), and follicular lymphoma (FL)[1]
- Many patients experience disease progression, which is sometimes caused by resistance mutations within BTK that arise during treatment with both covalent and noncovalent BTK inhibitors[2,3]
- BGB-16673, a chimeric degradation activating compound (CDAC), is a bivalent molecule comprising a BTK-binding moiety + linker + E3 ligase binder that induces BTK degradation via polyubiquitination (**Figure 1**)[4]
- In preclinical models, BGB-16673 degraded both wild-type and mutant forms of BTK regardless of whether the mutation is associated with covalent (C481S, C481F, C481Y, L528W, and T474I) or noncovalent (V416L, M437R, T474I, and L528W) inhibitors, leading to tumor suppression[4,5]
- BGB-16673 treatment led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue in the first-in-human phase 1 study, even at the lowest dose[6]
- Here, updated safety and efficacy results are presented in patients with FL, MZL, and WM in the ongoing CaDAnCe-101 study

Figure 1. BGB-16673: A BTK-Targeted CDAC[7]



CDAC, chimeric degradation activating compound; Ub, ubiquitin.

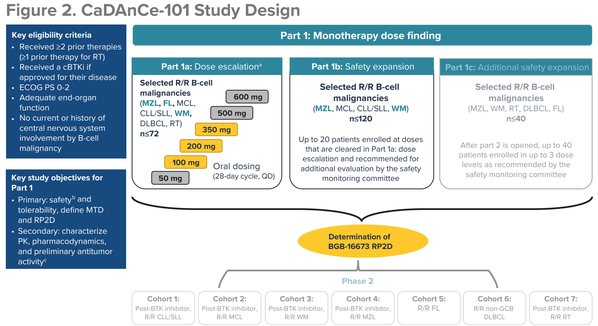
Attributes and Potential Advantages of BGB-16673

- 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)

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 relapsed/refractory (R/R) B-cell malignancies (**Figure 2**)
- Patients in this analysis had FL, MZL or WM and were treated in cohorts at 100 mg, 200 mg, or 350 mg per day until disease progression or unacceptable toxicity

Figure 2. CaDAnCe-101 Study Design

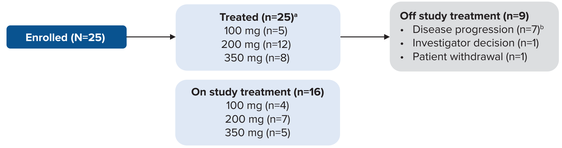


[a] Bayesian optimal interval design with 6 dose levels (50-600 mg orally QD). [b] Safety was assessed according to CTCAE v5.0 in all patients; DLTs were assessed during the first 4 weeks. [c] Response was assessed per Lugano 2014 criteria after 12 weeks in patients with FL and MZL and per IWWM-6 criteria after 4 weeks in patients with WM.[8,9]
cBTKi, covalent Bruton tyrosine kinase inhibitor; GCB, germinal center B-cell; RT, Richter transformation.

RESULTS

- As of February 14, 2024, a total of 25 patients with FL (n=7), MZL (n=5), and WM (n=13) had received BGB-16673, and 16 (64%) remained on treatment (**Figure 3**); median follow-up time was 5.85 months
- Patients were heavily pretreated, with a median of 4 (range, 2-11) prior lines of therapy (**Table 1**)

Figure 3. Patient Disposition



[a] Dose per day until disease progression or unacceptable toxicity. [b] Includes 1 patient who discontinued treatment due to an AE in the context of disease progression.

Table 1. Demographic and Baseline Characteristics

Parameter	All with FL/MZL/WM (N=25)
Age, median (range), years	72.0 (56-88)
Sex, n (%)	
Male	15 (60)
Female	10 (40)
ECOG performance status, n (%)	
0	10 (40)
1	14 (56)
2	1 (4)
Disease type, n (%)	
WM	13 (52)
FL	7 (28)
MZL	5 (20)
No. of prior lines of therapy, median (range)[a]	4 (2-11)
Prior covalent BTK inhibitor, n (%)	16 (64)
Prior noncovalent BTK inhibitor, n (%)	4 (16)
Discontinued BTK inhibitor due to PD, n/N (%)[b]	14/17 (82)
Prior BCL2 inhibitor, n (%)	6 (24)
***BTK* mutation present, n/N (%)**	2/14 (14)
Ann Arbor stage III/IV at study entry (FL/MZL), n/N (%)	9/12 (75)
IWWM stage (WM), n/N (%)[c]	
Low risk	3/13 (23)
Intermediate risk	5/13 (38)
High risk	4/13 (31)

[a] Must include prior anti-CD20 in patients with FL, WM, and MZL in the US and EU, and cBTKi in patients with WM in the US and EU, and in patients with MZL in the US. [b] One patient had prior treatment with noncovalent BTK inhibitor without prior covalent BTK inhibitor. [c] One patient had unknown risk.

Safety

- No cases of atrial fibrillation and 1 case of grade ≥3 hypertension were reported (an 88 year old patient with history of hypertension not on antihypertensives)
- One patient with MZL had a TEAE of pleural effusion in the context of PD that led to treatment discontinuation (**Table 2**)
- One patient with WM experienced a TEAE of septic shock in the context of PD that led to death, which was not considered treatment related by the investigator
- The most common TEAEs across dose groups were contusion (32%), fatigue, neutropenia/neutrophil count decreased, amylase increased, and upper respiratory tract infection (each 24%) (**Table 3**)
- The most common grade ≥3 TEAEs were neutropenia/neutrophil count decreased (n=5, 20%) and anemia (n=2, 8%)
- Five patients experienced grade ≥3 infections (1 in the context of PD and 1 possibly in the context of PD)
- No patients experienced a dose-limiting toxicity (DLT) during the DLT window (first 4 weeks of Part 1a)

Table 2. Overall Safety Summary

Patients, n (%)	All with FL/MZL/WM (N=25)
Any TEAE	24 (96)
Any treatment-related	18 (72)
Grade ≥3	13 (52)
Treatment-related grade ≥3	6 (24)
Serious	8 (32)
Treatment-related serious	0
Leading to death[a]	1 (4)
Treatment-related leading to death	0
Leading to treatment discontinuation[b]	1 (4)
Treatment-related leading to treatment discontinuation	0
Leading to treatment modification	5 (20)
Dose interruption	5 (20)
Dose reduction	0

[a] Septic shock (WM, 200 mg) in the context of possible disease progression. [b] Pleural effusion (MZL, 200 mg) in the context of disease progression.

Table 3. Most Common TEAEs (All Grade ≥10%)

Patients, n (%)	All With FL/MZL/WM (N=25) All Grade	Grade ≥3
Contusion	8 (32)	0
Neutropenia/neutrophil count decreased[a]	6 (24)	5 (20)
Upper respiratory tract infection	6 (24)	1 (4)
Amylase increased[b]	6 (24)	0
Fatigue	6 (24)	0
Lipase increased[b]	5 (20)	1 (4)
Anemia	4 (16)	2 (8)
Diarrhea	4 (16)	0
Dizziness	3 (12)	0
Dyspnea	3 (12)	1 (4)
Headache	3 (12)	0
Petechiae	3 (12)	0

[a] There were no cases of febrile neutropenia. [b] All events were lab findings and were transient, mostly occurring during the first 1-3 cycles of treatment, with no clinical pancreatitis. A total of 6 patients reported TEAEs of increased amylase or lipase.

Antitumor Activity

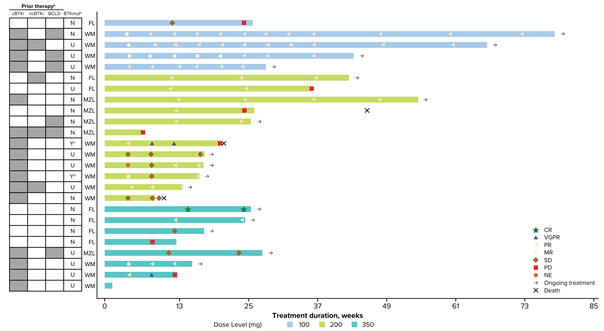
- In response-evaluable patients, the ORR was 75%
  - The ORR was 57% (4/7) in FL, 60% (3/5) in MZL, and 92% (11/12) in WM, including patients who had previously received a covalent BTK inhibitor (n=12; 11 WM, 1 MZL) and a noncovalent BTK inhibitor (n=3; 1 FL, 2 WM) (**Table 4**, **Figure 4**)
  - Disease control rate was 100% (12/12) in WM, 86% (6/7) in FL, and 80% (4/5) in MZL
  - Both patients with detected BTK mutations responded (WM; 200 mg; 1 PR, 1 VGPR)
- All patients with WM had a numerical reduction from baseline in IgM (**Figure 5**)

Table 4. Responses by Histology in Evaluable Patients

	WM (n=12)	FL (n=7)	MZL (n=5)
Best overall response, n (%)			
CR	0	1 (14)	0
VGPR	2 (17)	0	0
PR	9 (75)	3 (43)	3 (60)
SD	1 (8)	2 (29)	1 (20)
PD	0	1 (14)	1 (20)
Disease control rate, n (%)[a]	12 (100)	6 (86)	4 (80)
ORR, n (%)[b]	11 (92)	4 (57)	3 (60)
Time to first response, median (range), months[c]	0.95 (0.9-3.7)	2.71 (2.6-3.3)	2.83 (2.8-2.9)

[a] Proportion of patients with a best overall response of SD or higher. [b] Proportion of patients who achieved a best overall response better than SD.
[c] Time to first qualifying response in patients with a best overall response better than SD.
VGPR, very good PR.

Figure 4. Treatment Duration and Response Assessment

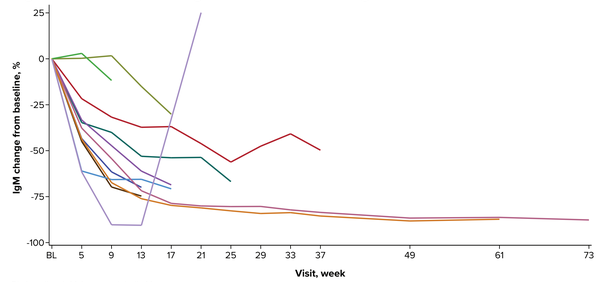


[a] Gray shading = patient had the indicated prior therapy. [b] BTK mutation status was classified as present (Y), absent (N), or unknown (U).
[c] Mutated L528F, L528W, C481S. [d] Mutated C481Y and C481S.
BCL2i, B-cell lymphoma 2 inhibitor; BTKi, covalent Bruton tyrosine kinase inhibitor; MR, minor response; mut, mutation; ncBTKi, noncovalent Bruton tyrosine kinase inhibitor, VGPR, very good PR.

CONCLUSIONS

- Updated data from this ongoing, first-in-human study show that the novel BTK degrader BGB-16673 appears to have a safe and tolerable profile, with no DLTs in patients with MZL, WM, or FL
  - Discontinuations due to TEAEs were low (1 of 25 patients)
  - No atrial fibrillation has been reported so far
- BGB-16673 had durable antitumor activity with a short time to response in heavily pretreated patients with NHL, including those with BTK inhibitor–resistant disease
  - In the high-risk heavily pretreated (median of 4 prior lines of therapy) population of patients with NHL, the ORR was 75%
  - The ORR was 57% in patients with FL, 60% in patients with MZL, and 92% in patients with WM
- These data support further investigation of the clinical activity of BGB-16673 in patients with NHL; dose finding and additional safety expansion (Part 1c) are ongoing and enrollment continues in the CaDAnCe-101 study

Figure 5. Percent Change From Baseline in IgM for Patients With WM

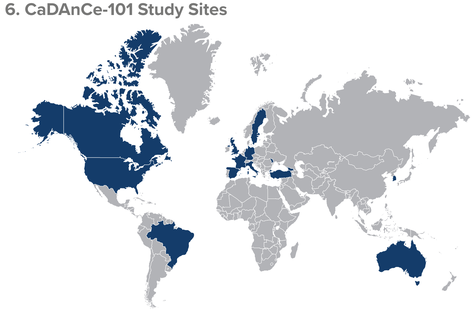


BL, baseline; IgM, Immunoglobulin M.

Study Status

- Enrollment for CaDAnCe-101 Part 1c and Phase 2 is ongoing at 90 of 110 planned study sites across the US, Canada, Brazil, the UK, France, Germany, Italy, Spain, Sweden, Moldova, Turkey, Georgia, South Korea and Australia (**Figure 6**)

Figure 6. CaDAnCe-101 Study Sites



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DISCLOSURES

CYC: Consultancy, honoraria, and membership on an entity's board of directors or advisory committees: Roche, Janssen, MSD, Gilead, Ascentage Pharma, AstraZeneca, Lilly. **JFS:** Honoraria, membership on an entity's board of directors or advisory committees, research funding and speakers bureau: AbbVie, AstraZeneca, Janssen, BMS, BeiGene, Gilead, Genor Bio, Roche; Consultancy: TG Therapeutics; Research funding: Roche. **ML:** Travel, accommodations, expenses: Celgene. **HE:** Research funding, honoraria, or consulting fees: AbbVie, Genentech, Kite, Gilead Sciences, Takeda, Acerta, AstraZeneca, BeiGene and Juno. **AMF:** Consulting or advisory role: AbbVie, BeiGene, AstraZeneca, Janssen; Travel, accommodations, expenses: AbbVie, BeiGene. **JNA:** Research funding: BeiGene, Celgene/BMS, Genentech, Janssen, Pharmacyclics, Regeneron; Consultancy: AbbVie, Adaptive Biotechnologies, ADC Therapeutics, AstraZeneca, BeiGene, Genentech, Janssen, Lilly, NeoGenomics, Pharmacyclics; Speakers bureau: AbbVie, BeiGene, Janssen, Pharmacyclics; Other: Merck. **VTGL:** Research funding: BeiGene, Pfizer, Merck, AstraZeneca, GSK, AVEO, LOXO@Lilly, Regeneron, Genentech. **JT:** Research funding: BeiGene, Janssen, Pharmacyclics, Roche, Celgene/BMS, Selectar; Consulting or advisory role: BeiGene. **RA:** Writing support: BeiGene; Consulting fees: Roche/Genentech, Merck, ADC Therapeutics, BeiGene; Travel support: Roche; Advisory board: Merck. **XC, KB, JCP, AA:** Employment and may hold stock: BeiGene. **SF:** Current employment and current equity holder in publicly traded company: BeiGene; ended employment in the past 24 months: BMS. **CST:** Research funding: Janssen, AbbVie, BeiGene; Honoraria: Janssen, AbbVie, BeiGene, Loxo, AstraZeneca.

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