Updated Efficacy/Safety of Bruton Tyrosine Kinase Degrader BGB-16673 in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma: Ongoing Phase 1 CaDAnCe-101 Results

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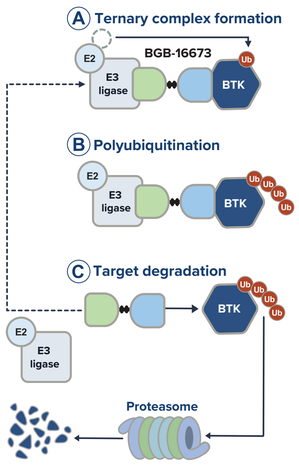
CONCLUSIONS

- Updated data from this ongoing phase 1/2 study show that the novel BTK degrader BGB-16673 was well tolerated, with a low rate of discontinuations due to TEAEs
- BGB-16673 had encouraging antitumor activity with a short time to response in heavily pretreated patients with NHL, including those with BTK inhibitor–resistant disease
  - The ORR was 50% (10/20) in patients with MZL and 42% (5/12) in evaluable patients with FL
  - Three patients achieved CR (MZL, n=2; FL, n=1)
  - Disease control rate was 75% (15/20) in patients with MZL and 67% (8/12) in those with FL
- These data support further investigation of BGB-16673 clinical activity in patients with FL and MZL

INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibition is effective in indolent non-Hodgkin lymphoma (NHL),[1,2] but disease invariably relapses
- 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 (**Figure 1**)[3,4]
- In preclinical models, BGB-16673 showed central nervous system penetration and degraded wild-type and mutant BTK resistant to covalent (C481S, C481F, C481Y, L528W, and T474I) and noncovalent (V416L, M437R, T474I, and L528W) BTK inhibitors[4,5]
- In the ongoing phase 1/2 CaDAnCe-101 study (BGB-16673-101, NCT05006716), BGB-16673 monotherapy was well tolerated in heavily pretreated patients with follicular lymphoma (FL) or marginal zone lymphoma (MZL), with no dose-limiting toxicities at doses up to 500 mg once daily[6]
  - The maximum tolerated dose has not been reached
  - Additionally, BGB-16673 led to durable antitumor activity, with a short time to response in heavily pretreated patients with NHL, including those with BTK inhibitor–resistant disease[6]
- Here, updated results in patients with FL and MZL enrolled in CaDAnCe-101 are presented

Figure 1. BGB-16673: A BTK-Targeted CDAC[3]



Attributes and Potential Advantages of BGB-16673

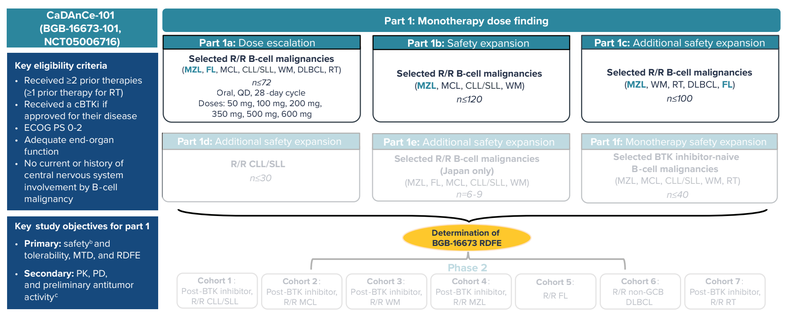
- Catalytic pharmacology that does not require sustained target binding
- Can interrupt formation of oncogenic protein complexes (scaffolding)
- CNS penetration observed in preclinical studies
- Potential to overcome resistance mutations (eg, BTK C481S, C481F, C481Y, L528W, and V416L)
- No immunomodulatory drug activity observed

Abbreviations: BTK, Bruton tyrosine kinase; CDAC, chimeric degradation activating compound; CNS, central nervous system; 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 relapsed/refractory B-cell malignancies (**Figure 2**)

Figure 2. CaDAnCe-101 Study Design[a]



[a]Data from gray portions of the figure are not included in this presentation. [b]Safety was assessed according to CTCAE v5.0 in all patients. [c]Response was assessed per Lugano 2014 criteria after 12 weeks.[7]

Abbreviations: BTK, Bruton tyrosine kinase; cBTKi, covalent BTK inhibitor; 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; 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 March 3, 2025, 17 patients with FL and 29 with MZL had received BGB-16673
- Patients were heavily pretreated, with a median of 3 prior lines of therapy for both FL (range, 2-9) and MZL (range 1-9) (**Table 1**)
- The median study follow-up was 3.4 months (range, 0.7-29.9 months) and 8.0 months (range, 0.3-25.1 months) in the FL and MZL cohorts, respectively

Table 1. Baseline Demographics and Disease Characteristics

	FL (n=17)	MZL (n=29)
Age, median (range), years	70 (52-86)	75 (33-88)
Male, n (%)	13 (76.5)	13 (44.8)
ECOG PS, n (%)		
0	8 (47.1)	16 (55.2)
1	9 (52.9)	13 (44.8)
Ann Arbor stage III/IV at study entry, n/N (%)[a]	14/16 (87.5)	23/24 (95.8)
Tumor bulk, n (%)		
Longest diameter ≥5 cm	6 (35.3)	6 (20.7)
No. of prior lines of therapy, median (range)	3.0 (2-9)	3.0 (1-9)
Prior therapy, n (%)		
cBTK inhibitor	2 (11.8)	25 (86.2)
ncBTK inhibitor	1 (5.9)	4 (13.8)
BCL2 inhibitor	0	7 (24.1)
Anti-CD20–based therapy	17 (100)	29 (100)
Chemotherapy	16 (94.1)	28 (96.6)
Discontinued prior BTK inhibitor due to PD, n/N (%)	3/3 (100)	21/25 (84.0)[b]

[a]Excludes patients with unknown status. [b]Reasons for five discontinuations of BTK inhibitor apart from PD were toxicity (n=3) and other (n=1); one patient in the MZL cohort had an adverse event in the context of progressive disease.

Abbreviations: BCL2, B-cell lymphoma 2; cBTK, covalent Bruton tyrosine kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; MZL, marginal zone lymphoma; ncBTK, noncovalent Bruton tyrosine kinase; PD, progressive disease.

- Five patients with MZL had a treatment-emergent adverse event (TEAE) that led to treatment discontinuation (pleural effusion in the context of progressive disease; hepatocellular carcinoma; and treatment-related TEAEs of intracranial hemorrhage, rhabdomyolysis, and pulmonary aspergillosis; n=1 each; **Table 2**)
  - One patient had a TEAE (intracranial hemorrhage) leading to death
- One patient with FL had a treatment-related TEAE of cardiac arrest which led to both treatment discontinuation and death
- The most common TEAEs were upper respiratory tract infection in the FL group and neutropenia and fatigue in the MZL group (**Table 3**); across both histologies, neutropenia was the most frequently reported grade ≥3 TEAE
- One patient each in the FL and MZL groups had a grade 3 TEAE of hypertension; the patient in the MZL group had a history of hypertension
- Three patients in the MZL group experienced major hemorrhage (gastrointestinal, intracranial, and hemothorax; n=1 each)
- Six patients (FL, n=2; MZL, n=4) experienced grade ≥3 infection

Table 2. Overall Safety Summary

Patients, n (%)	FL (n=17)	MZL (n=29)
Any TEAE	16 (94.1)	29 (100)
Any treatment-related	9 (52.9)	22 (75.9)
Grade ≥3	5 (29.4)	13 (44.8)
Treatment-related grade ≥3	3 (17.6)	8 (27.6)
Serious	3 (17.6)	10 (34.5)
Treatment-related serious	2 (11.8)	3 (10.3)
Leading to death	1 (5.9)	1 (3.4)
Treatment-related leading to death	1 (5.9)	1 (3.4)
Leading to treatment discontinuation	1 (5.9)	5 (17.2)
Treatment-related leading to treatment discontinuation	1 (5.9)	3 (10.3)
Leading to treatment modification	6 (35.3)	9 (31.0)
Dose interruption	6 (35.3)	9 (31.0)

Abbreviations: FL, follicular lymphoma; MZL, marginal zone lymphoma; TEAE, treatment-emergent adverse event.

Table 3. TEAEs in ≥3 Patients in Either Group

	FL (n=17)		MZL (n=29)	
Patients, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Upper respiratory tract infection	4 (23.5)	1 (5.9)	4 (13.8)	0
Fatigue	3 (17.6)	0	7 (24.1)	0
Contusion (bruising)	3 (17.6)	0	6 (20.7)	0
Diarrhea	3 (17.6)	0	4 (13.8)	0
Thrombocytopenia[a]	2 (11.8)	1 (5.9)	3 (10.3)	0
Neutropenia[b]	2 (11.8)	2 (11.8)	8 (27.6)	6 (20.7)
Lipase increased	1 (5.9)	0	4 (13.8)	0
Amylase increased	1 (5.9)	0	3 (10.3)	0
Anemia	1 (5.9)	0	3 (10.3)	1 (3.4)
COVID-19	1 (5.9)	0	3 (10.3)	1 (3.4)
Headache	1 (5.9)	0	3 (10.3)	0
Pyrexia	1 (5.9)	0	4 (13.8)	0
Asthenia	0	0	4 (13.8)	1 (3.4)
Petechiae	0	0	4 (13.8)	0
Decreased appetite	0	0	3 (10.3)	0
Hematoma	0	0	3 (10.3)	0

[a]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*. [b]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*.

Abbreviations: FL, follicular lymphoma; MZL marginal zone lymphoma; TEAE, treatment-emergent adverse event.

- In response-evaluable patients, the investigator-assessed overall response rate (ORR) was 50.0% (10/20) in patients with MZL and 41.7% (5/12) in patients with FL (**Table 4** and **Figure 4**)
  - Three patients achieved CR (MZL, n=2; FL, n=1)
  - Responses were also seen in patients with MZL who had previously received a covalent BTK inhibitor (8/18)
- The disease control rate was 75.0% (15/20) in patients with MZL and 66.7% (8/12) in patients with FL

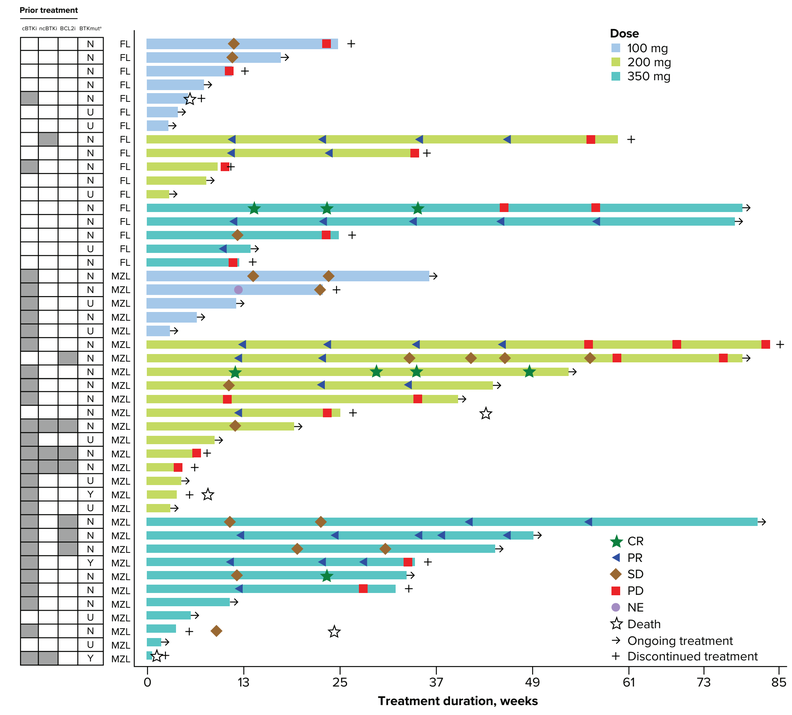
Table 4. Responses by Histology

	FL (n=12)	MZL (n=20)
Best overall response, n (%)		
CR	1 (8.3)	2 (10.0)
PR	4 (33.3)	8 (40.0)
SD	3 (25.0)	5 (25.0)
PD	3 (25.0)	3 (15.0)
ORR, n (%)[a]	5 (41.7)	10 (50.0)
Disease control rate, n (%)[b]	8 (66.7)	15 (75.0)
Time to first response, median (range), months[c]	2.6 (2.3-3.3)	2.9 (2.6-9.9)
Duration of response, median (95% CI), months[c]	9.5 (5.7-NE)	10.8 (2.8-NE)

[a]Includes best overall responses of PR or CR. [b]Includes best overall responses of SD or better. [c]In patients with best overall response better than SD.

Abbreviations: CR, complete response; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 3. Treatment Duration and Response



[a]BTK mutation status is classifed as yes (Y), no (N), or unknown (U).

Abbreviations: BCL2i; B-cell lymphoma 2 inhibitor; BTK, Bruton tyrosine kinase; BTKmut, mutated BTK; cBTKi, covalent BTK inhibitor; CR, complete response; FL, follicular lymphoma; MZL, marginal zone lymphoma; ncBTKi, noncovalent BTK inhibitor; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease.

STUDY STATUS

- Enrollment for CaDAnCe-101 phase 1 and phase 2 is ongoing at >100 study sites across the US, Canada, UK, France, Georgia, Germany, Italy, Moldova, Spain, Sweden, Turkey, Australia, South Korea, Brazil, and Japan

REFERENCES

1. Noy A, et al. *Blood*. 2017;129(16):2224-2232.
2. Zinzani PL, et al. *J Clin Oncol*. 2023;41(33):5107-5117.
3. Chirnomas D, et al. *Nat Rev Clin Oncol*. 2023;20(4):265-278.
4. Feng X, et al. EHA 2023. Abstract P1239.
5. Wang H, et al. EHA 2023. Abstract P1219.
6. Tam CS, et al. ASH 2024. Abstract 1649.
7. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-3068.

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