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 CaDAnCe-101 Study

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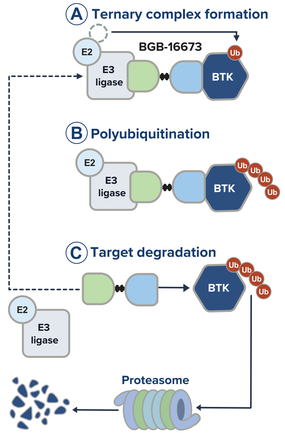
INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibition is effective in indolent non-Hodgkin lymphoma (NHL)[1,2], but disease invariably relapses
- BGB-16673 is a bivalent small molecule that induces BTK degradation by binding specifically to BTK and the E3 ligase (**Figure 1**)[3]
- In preclinical models, BGB-16673 degraded wild-type and mutant forms of BTK associated with resistance to covalent (C481S, C481F, C481Y, L528W, and T474I) and noncovalent (V416L, M437R, T474I, and L528W) BTK inhibitors, leading to tumor suppression[3,4]
- BGB-16673 treatment led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue in CaDAnCe-101, the ongoing first-in-human study[5]
- BGB-16673 is being investigated in a variety of B-cell malignancies including follicular lymphoma (FL) and marginal zone lymphoma (MZL)
- Updated safety and efficacy results from phase 1 of CaDAnCe-101 are presented here

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



Attributes and Potential Advantages of BGB-16673

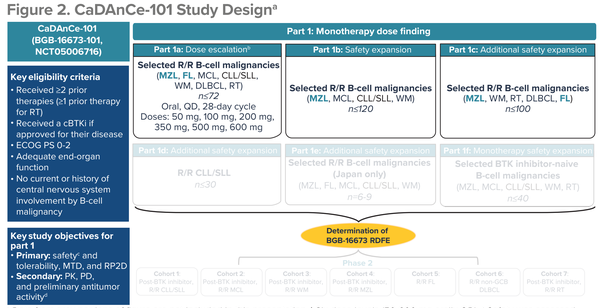
- Catalytic pharmacology that does not require sustained target binding
- Can interrupt formation of oncogenic protein complexes (scaffolding)
- Can penetrate the blood brain barrier
- Potential to overcome resistance mutations (eg, BTK C481S, C481F, C481Y, L528W, and V416L)
- Substantially reduced immunomodulatory 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 relapsed/refractory (R/R) B-cell malignancies (**Figure 2**)

Figure 2. CaDAnCe-101 Study Design[a]



[a] Data from gray portions of figure are not included in this presentation. [b] Six dose levels (50-600 mg orally QD). [c] Safety was assessed according to CTCAE v5.0 in all patients; DLTs were assessed during the first 4 weeks of part 1a. [d] Response was assessed per Lugano 2014 criteria after 12 weeks.[6]
cBTKi, covalent Bruton tyrosine kinase inhibitor; GCB, germinal center B-cell; PD, pharmacodynamics; RT, Richter transformation.

RESULTS

- As of September 2, 2024, 25 patients with FL (n=8) and MZL (n=17) had received BGB-16673
- Patients were heavily pretreated, with a median of 4.5 (range, 2-9) and 3 (2-7) prior lines of therapy for FL and MZL, respectively (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics

	FL (n=8)	MZL (n=17)
Age, median (range), years	68 (57-75)	75 (41-88)
Male, n (%)	7 (87.5)	9 (52.9)
ECOG PS, n (%)		
0	3 (37.5)	11 (64.7)
1	5 (62.5)	6 (35.3)
Ann Arbor stage III/IV at study entry, n/N (%)	6/7 (85.7)	16/16 (100)
Tumor bulk, n (%)		
Longest diameter ≥5 cm	4 (50.0)	4 (23.5)
No. of prior lines of therapy, median (range)	4.5 (2-9)	3 (2-7)
Prior therapy, n (%)		
cBTK inhibitor	1 (12.5)	15 (88.2)
ncBTK inhibitor	1 (12.5)	1 (5.9)
BCL2 inhibitor	0	5 (29.4)
Anti-CD20–based therapy	8 (100)	12 (100)
Chemotherapy	8 (100)	12 (100)
Discontinued prior BTK inhibitor due to PD, n/N (%)	2/2 (100)	11/15 (73.3)[a]

[a] Four remaining patients discontinued prior BTK inhibitor due to toxicity (n=3) and surgical procedure (n=1).
cBTK, covalent BTK; ncBTK, noncovalent BTK.

- Three patients with MZL had a treatment-emergent adverse event (TEAE) that led to treatment discontinuation (pleural effusion in the context of PD, rhabdomyolysis, pulmonary aspergillosis; n=1 each) (**Table 2**)
- TEAEs in ≥2 patients are shown in **Table 3**; no grade ≥3 TEAEs occurred in >1 patient
- One patient with a history of hypertension in the MZL group had grade 3 hypertension (monitored without treatment); 1 patient had grade 1 atrial fibrillation
- One patient in the MZL group experienced major hemorrhage (hemothorax post thoracoscopic surgery with pleurodesis)
- Three patients (FL, n=1; MZL, n=2) experienced grade ≥3 infections
- No febrile neutropenia occurred
- No DLT occurred during the first 4 weeks of part 1a; the MTD was not reached
- Dose escalation stopped at 500 mg based on the pharmacodynamic profile

Table 2. Overall Safety Summary

Patients, n (%)	FL (n=8)	MZL (n=17)
Any TEAE	8 (100)	16 (94.1)
Any treatment-related	5 (62.5)	11 (64.7)
Grade ≥3	2 (25.0)	7 (41.2)
Treatment-related grade ≥3	1 (12.5)	3 (17.6)
Serious	1 (12.5)	6 (35.3)
Treatment-related serious	0	2 (11.8)
Leading to death	0	0
Leading to treatment discontinuation	0	3 (17.6)
Treatment-related leading to treatment discontinuation	0	2 (11.8)

Table 3. TEAEs in ≥2 Patients in Either Group

	FL (n=8)		MZL (n=17)	
Patients, n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Upper respiratory tract infection	4 (50.0)	1 (12.5)	1 (5.9)	0
Fatigue	3 (37.5)	0	3 (17.6)	0
Contusion (bruising)	1 (12.5)	0	3 (17.6)	0
Headache	1 (12.5)	0	2 (11.8)	0
Lipase increased	1 (12.5)	0	2 (11.8)	0
Neutropenia[a]	1 (12.5)	1 (12.5)	2 (11.8)	1 (5.9)
Pyrexia	1 (12.5)	0	2 (11.8)	0
Thrombocytopenia[b]	1 (12.5)	1 (12.5)	2 (11.8)	1 (5.9)
Asthenia	0	0	2 (11.8)	0
Dyspnea	0	0	2 (11.8)	1 (5.9)
Flank pain	0	0	2 (11.8)	0
Hematoma	0	0	2 (11.8)	0
Mouth hemorrhage	0	0	2 (11.8)	0
Petechiae	0	0	2 (11.8)	0

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

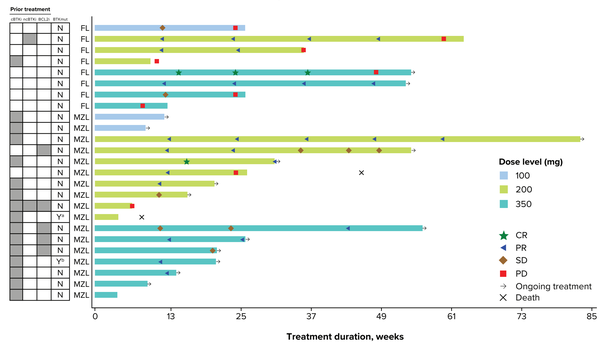
- In response-evaluable patients, the ORR was 50.0% (4/8) in FL and 64.3% (9/14) in MZL, which included patients previously treated with a covalent BTK inhibitor (0/1 in FL; 7/12 in MZL) and a noncovalent BTK inhibitor (1/1 in FL; 0/1 in MZL) (**Table 4** and **Figure 3**)
- Two patients (FL, n=1; MZL, n=1) achieved CR at the first disease assessment (12 weeks); 1 patient maintained their response through week 37
- Disease control rate was 75% (6/8) in FL and 78.6% (11/14) in MZL

Table 4. Responses by Histology

	FL (n=8)	MZL (n=14)[a]
Best overall response, n (%)		
CR	1 (12.5)	1 (7.1)
PR	3 (37.5)	8 (57.1)
SD	2 (25.0)	2 (14.3)
PD	2 (25.0)	1 (7.1)
ORR, n (%)[b]	4 (50.0)	9 (64.3)
Disease control rate, n (%)[c]	6 (75.0)	11 (78.6)
Follow-up time, median, months[d]	14.4 (3.3-24.0)	4.8 (1.9-19.1)
Time to first response, median (range), months[e]	2.7 (2.6-3.3)	2.8 (2.5-9.9)

[a] Three patients were not yet response evaluable. [b] Includes best overall responses of PR or CR. [c] Includes best overall responses of SD or better. [d] For all enrolled patients: FL, n=8; MZL, n=17. [e] In patients with a best overall response better than SD.

Figure 3. Treatment Duration and Response



BTK mutation status (Y/N) is listed.
[a] BTK mutation: C481Y. [b] BTK mutation: E41K.

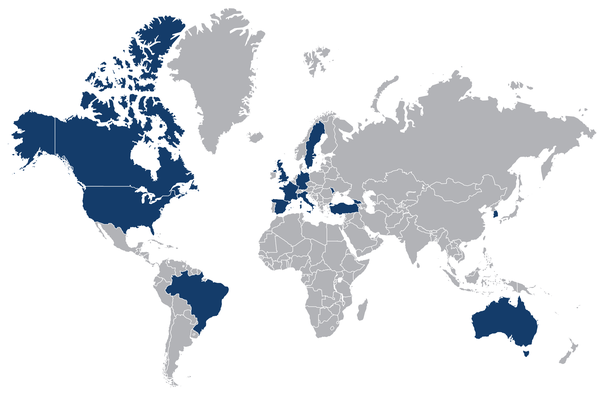
CONCLUSIONS

- Updated data from this ongoing study show that the novel BTK degrader BGB-16673 was safe and tolerable in heavily pretreated patients with FL or MZL; no DLTs occurred and MTD was not reached with dose escalation up to 500 mg
  - Discontinuations due to TEAEs were low; 1 patient discontinued in the context of PD
- BGB-16673 had durable antitumor activity with a short time to response in heavily pretreated patients with NHL, including those with BTK inhibitor–exposed disease
  - ORR was 50.0% in FL and 64.3% in MZL
  - Two patients achieved CR (FL, n=1; MZL, n=1)
- These data support further investigation of BGB-16673 clinical activity in patients with NHL; enrollment in CaDAnCe-101 continues for FL and MZL

Study Status

- Enrollment for CaDAnCe-101 phase 1 and phase 2 is ongoing at >90 study sites across the US, Canada, UK, France, Georgia, Germany, Italy, Moldova, Spain, Sweden, Turkey, Australia, South Korea, and Brazil (**Figure 4**)

Figure 4. CaDAnCe-101 Study Sites (Recruiting)



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. Feng X, et al. EHA 2023. Abstract P1239.
4. Wang H, et al. EHA 2023. Abstract P1219.
5. Seymour JF, et al. ASH 2023. Abstract 4401.
6. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-3067.

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