CaDAnCe-102

Preliminary Safety and Efficacy of Bruton Tyrosine Kinase Degrader BGB-16673 in Patients with Relapsed/Refractory B-Cell Malignancies: Results From CaDAnCe-102 (BGB-16673-102)

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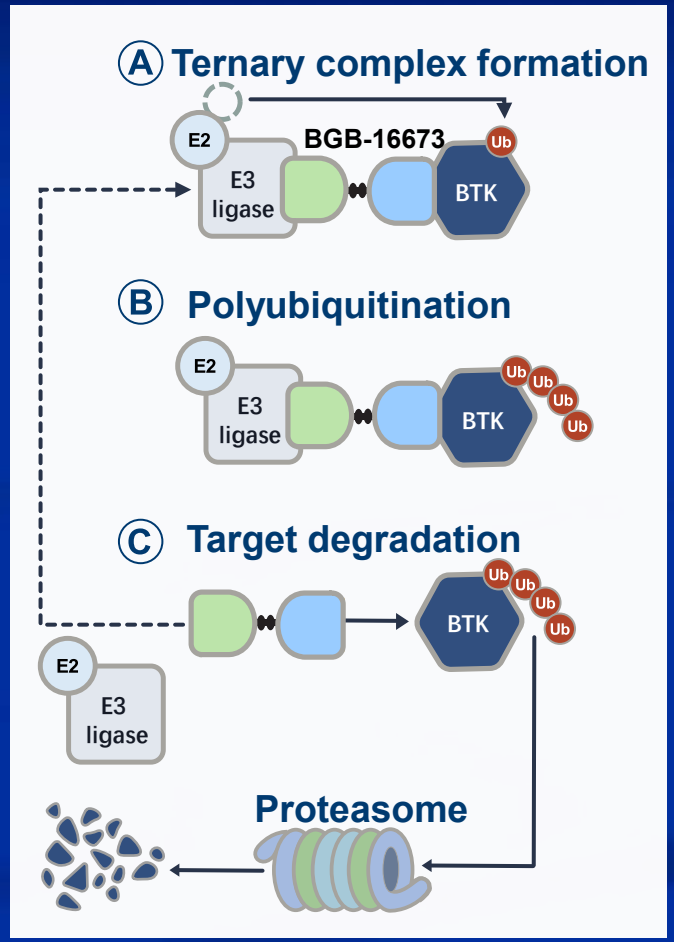
Disclosures for Ying Qian

- Nothing to disclose

BGB-16673: A Chimeric Degradation Activating Compound (CDAC)

- cBTK inhibitors have transformed the therapeutic landscape for B-cell malignancies, including CLL, MCL, MZL, and WM, but treatment resistance due to BTK mutations is an emerging challenge in clinical practice that necessitates novel therapy options[1,2]
- 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[3]
- In preclinical models, BGB-16673 showed CNS penetration and degraded both wild-type and mutant BTK resistant to cBTK (C481S, C481F, C481Y, L528W, T474I) and ncBTK inhibitors (V416L, M437R, T474I, L528W)[3,4]
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue[5]
- Here, preliminary safety and efficacy data in Chinese patients with R/R B-cell malignancies in phase 1 of CaDAnCe-102 are presented



BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CNS, central nervous system; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ncBTK, noncovalent Bruton tyrosine kinase; R/R, relapsed/refractory; ub, ubiquitin; WM, Waldenström macroglobulinemia.

1. Pal Singh S, et al. *Mol Cancer*. 2018;17(1):57; 2. Wang E, et al. *N Engl J Med*. 2022;386(8):735-743; 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.

CaDAnCe-102: A Multicenter, Open Label, Phase 1/2 Study in R/R B-cell Malignancies in China

CaDAnCe-102 study design
(BGB-16673-102; NCT05294731)

Key eligibility criteria

- Diagnosed with a R/R B-cell malignancy (CLL/SLL, WM, MCL, MZL, non-GCB DLBCL, FL, RT)
- ≥1 prior therapy (≥2 prior therapies for FL, WM, or MZL), including a BTK inhibitor for CLL/SLL, WM, or MCL
- ECOG PS 0-2
- Adequate organ function

Key study objectives

- **Primary:** safety/tolerability[b], MTD, RP2D
- **Secondary:** PK, PD, ORR[c]

Phase 1: Monotherapy dose finding

Phase 1a: Dose escalation

Selected R/R B-cell malignancies
(CLL/SLL, WM, MCL, MZL, non-GCB DLBCL, FL, RT)

Oral, QD, 28-day cycle[a]
Doses: 50 mg, 100 mg, 200 mg, 350 mg, 500 mg

Phase 1b: Safety expansion

Selected R/R B-cell malignancies
(CLL/SLL, WM, MCL, MZL, non-GCB DLBCL, FL, RT)

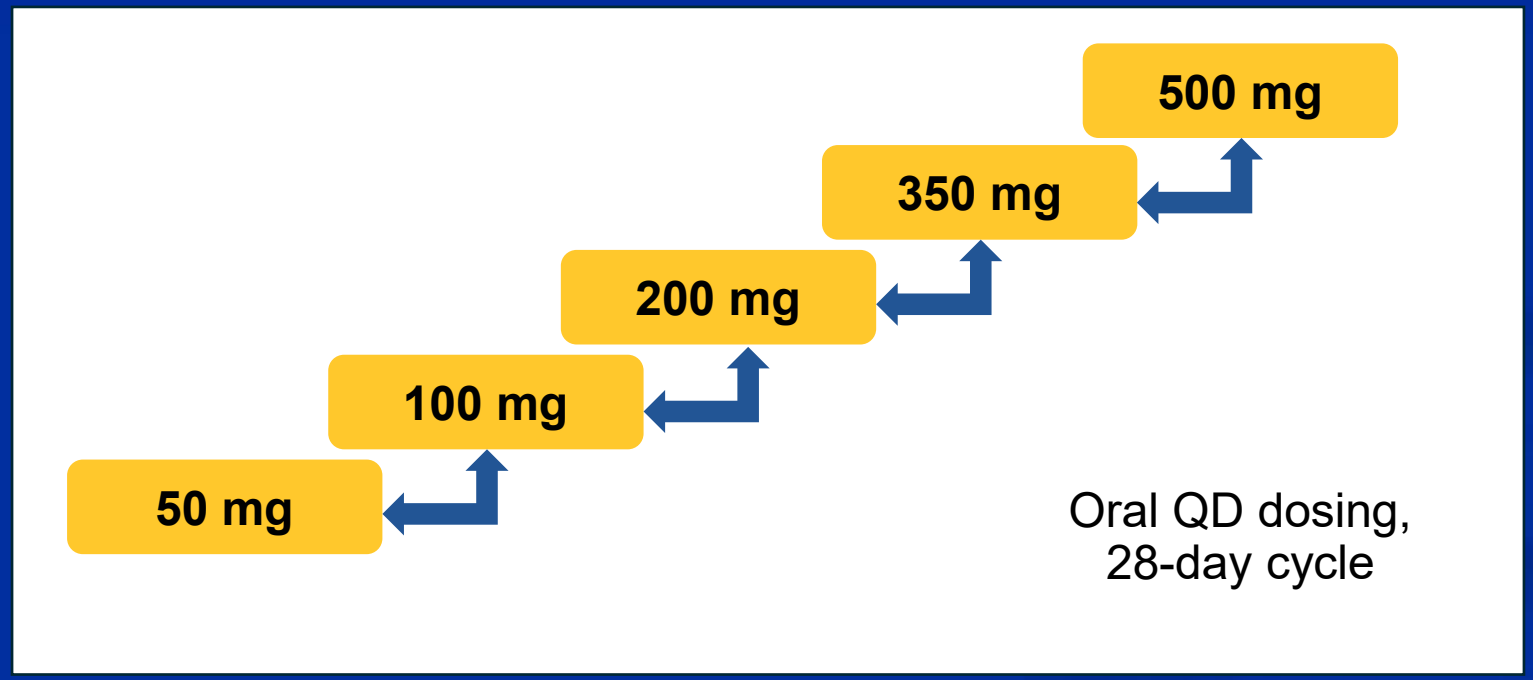
Determination of BGB-16673 RP2D

→ Phase 2

[a]Treatment was administered until progression, intolerance, or other criteria were met for treatment discontinuation. [b]Safety was assessed according to NCI-CTCAE v5.0 in all patients and iwCLL hematologic toxicity criteria in patients with CLL. [c]Responses were assessed per Lugano criteria for SLL, DLBCL, FL, RT, MZL, and MCL; iwCLL 2018 criteria for CLL; and iwWM-11 criteria for WM.
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GCB, germinal center B-cell; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; iwWM, Internal Workshop on Waldenström Macroglobulinemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; ORR, overall response rate PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; RT, Richter transformation; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

Phase 1a Dose Escalation

- Up to the highest dose tested (500 mg), no DLTs occurred
- The RP2D for patients with R/R CLL/SLL was determined to be 200 mg



CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLT, dose-limiting toxicity; QD, once daily; RP2D, recommended phase 2 dose; R/R, relapsed/refractory.

Baseline Patient Characteristics

- As of April 11, 2025, 55 patients were enrolled and treated; 24 patients remained on treatment

	Total (N=55)
Study follow-up, median (range), months	7.4 (0.6-34.2)
Age, median (range), years	63 (25-82)
Male, n (%)	40 (72.7)
ECOG PS, n (%)	
0	24 (43.6)
1	27 (49.1)
2	4 (7.3)
Disease type, n (%)	
MCL	15 (27.3)
MZL	12 (21.8)
DLBCL	11 (20.0)
CLL/SLL	7 (12.7)
FL	5 (9.1)
WM	5 (9.1)

	Total (N=55)
No. of prior lines of therapy, median (range)	3 (1-7)
Prior therapy, n (%)	
Chemotherapy	52 (94.5)
Anti-CD20–based therapy	50 (90.9)
cBTK inhibitor	36 (65.5)
Immunomodulatory drugs	17 (30.9)
BCL2 inhibitor	7 (12.7)
ncBTK inhibitor	1 (1.8)
Mutation status, n/N tested (%)	
del(17p)[a] or *TP53* mutation	26/29 (89.7)
TP53 mutation	26/41 (63.4)
BTK mutation	7/41 (17.1)
PLCG2 mutation	3/41 (7.3)
BCL2 mutation	4/41 (9.8)
del(11q)[a]	0/7 (0)

Data cutoff: April 11, 2025.
[a]Only tested in patients with R/R CLL/SLL.
BCL2, B-cell lymphoma 2; 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; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ncBTK, noncovalent Bruton tyrosine kinase; R/R, relapsed/refractory; WM, Waldenström macroglobulinemia.

Overall Safety Summary

- No DLTs occurred[a]
- None of the TEAEs that led to death were considered related to treatment by the investigators

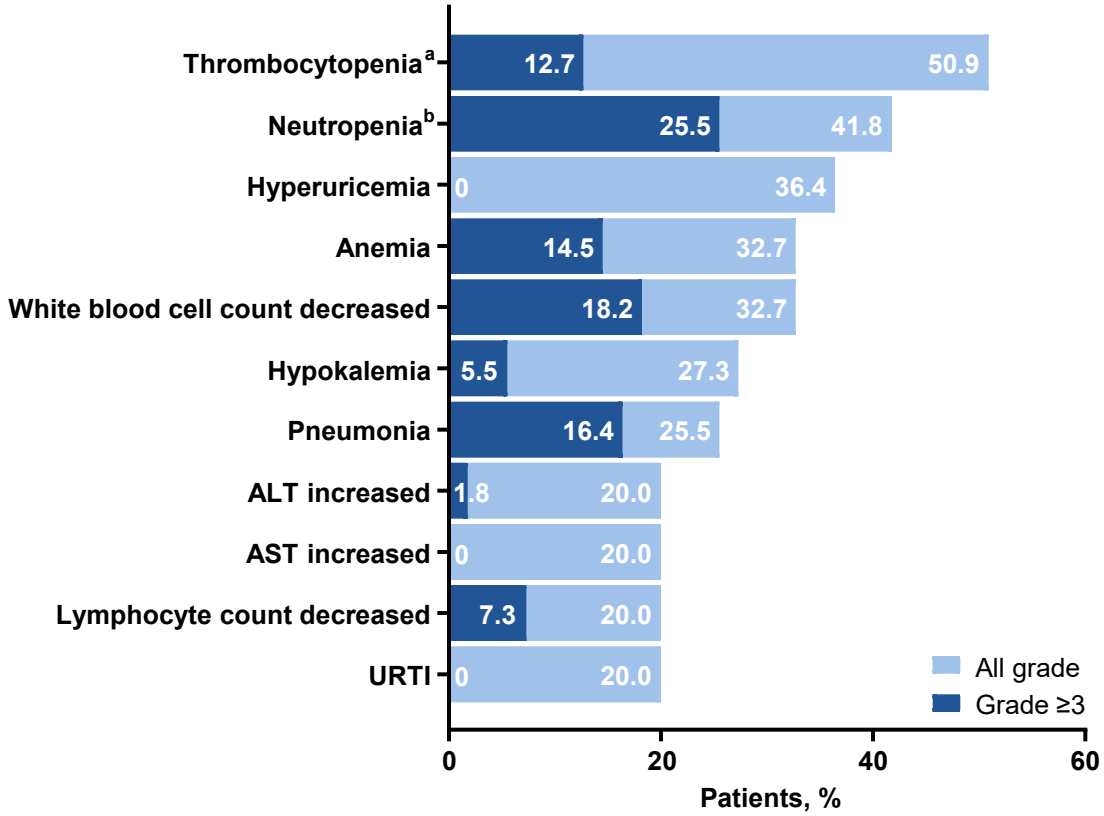
Patients, n (%)	Total (N=55)
Any TEAE	54 (98.2)
Any treatment-related	52 (94.5)
Grade ≥3	36 (65.5)
Treatment-related grade ≥3	27 (49.1)
Serious	24 (43.6)
Treatment-related serious	11 (20.0)
Leading to death[b]	4 (7.3)
Treatment-related leading to death	0
Leading to treatment discontinuation[c]	2 (3.6)
Treatment-related leading to treatment discontinuation	0
Leading to dose reduction[d]	2 (3.6)
Treatment-related leading to dose reduction	2 (3.6)

[a]DLTs were only assessed during the first 4 weeks of part 1a. [b]COVID-19 pneumonia, n=1 (100 mg); pneumonia, n=1 (200 mg); cardiac failure, n=1 (200 mg); bronchopulmonary aspergillosis and respiratory failure secondary to COVID-19 pneumonia, n=1 (350 mg). [c]COVID-19 pneumonia, n=1 (100 mg); pneumonia and pulmonary infarction, n=1 (50 mg). [d]Purpura, n=1; pyrexia, n=1 (both treated at 350 mg).
DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse event.

TEAEs Reported in CaDAnCe-102 Phase 1

- Hypertension: n=4 (all grade 1/2 except for 1 patient with grade 3 hypertension)
- Grade 3 hemorrhage: n=2 (both due to an alternative cause unrelated to BGB-16673, as assessed by the investigator; no grade 4 or 5 hemorrhage reported)
- Febrile neutropenia: n=1 (in the context of COVID-19)
- No atrial fibrillation occurred

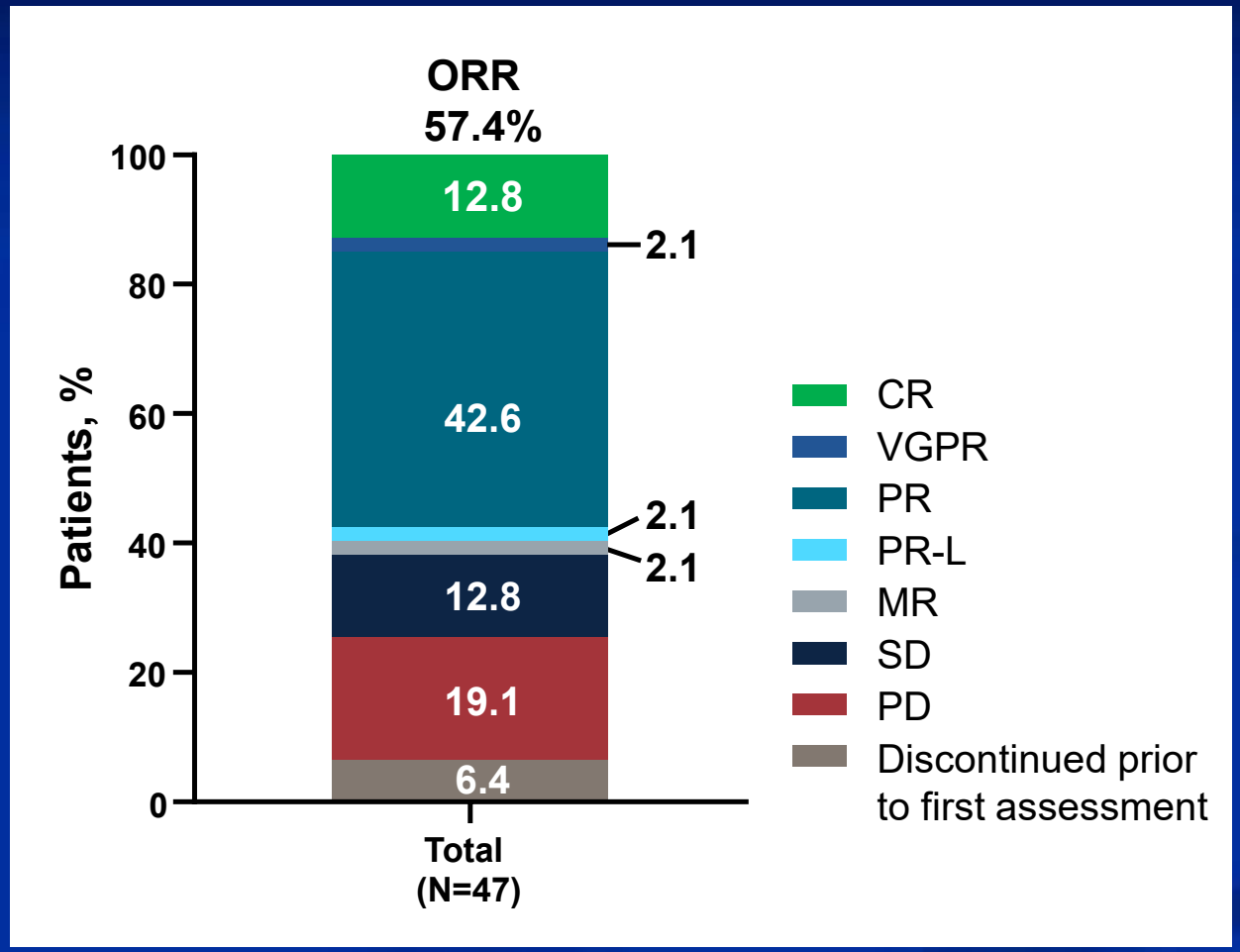
All-Grade TEAEs in ≥20% of All Patients



[a]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*. [b]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

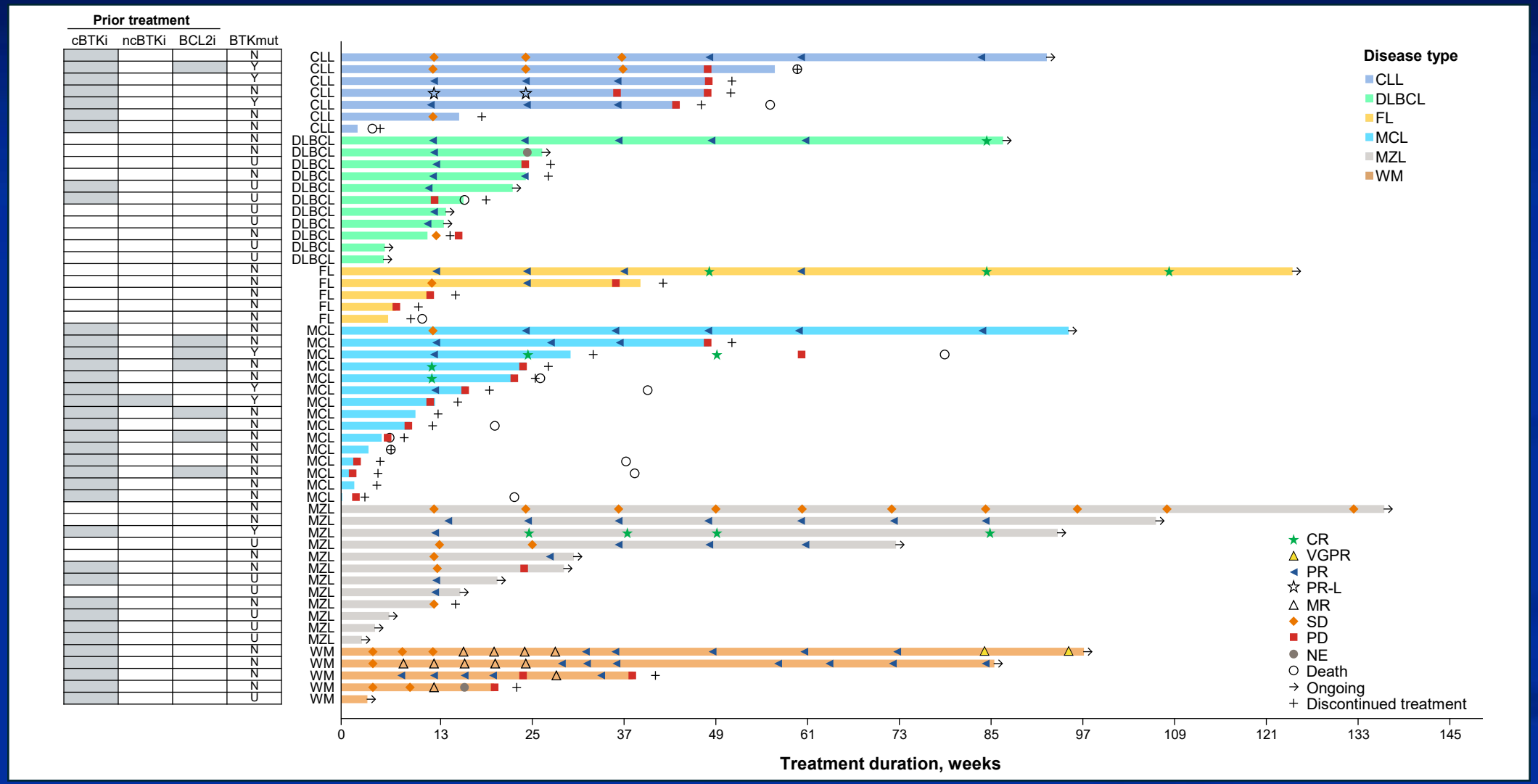
Overall Response Rate[a]

- In 47 response-evaluable[b] patients, the ORR was 57.4%
- Six patients (12.8%) had a CR:
  - MCL, n=3 (includes 1 patient who was heavily pretreated with 7 prior lines of therapy)
  - DLBCL, FL, and MZL, n=1 each
- One patient with WM who had 4 prior lines of therapy had a VGPR
- Median time to first response was 2.8 months (range, 1.8-11.1 months)[c]
- Median time to best response was 2.9 months (range, 1.8-19.4 months)
- Median duration of exposure was 4.6 months (range, 0-31.4 months)



[a]Best overall response of PR or better. [b]Patients who received ≥1 dose of BGB-16673, had 1 baseline and ≥1 postbaseline disease assessments, or died or experienced progressive disease. Patients without any postbaseline disease assessment who discontinued the study due to AEs prior to their first disease assessment, or who were lost to follow-up, were also included. [c]In patients with best overall response of MR or better.
AE, adverse event; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MR, minor response; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

Treatment Duration and Response Assessment



BCL2i, B-cell lymphoma 2 inhibitor; BTK, Bruton tyrosine kinase; cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic lymphoma; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MR, minor response; mut, mutation; MZL, marginal zone lymphoma; ncBTKi, noncovalent Bruton tyrosine kinase inhibitor; NE, not evaluable; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

Conclusions

- Preliminary data from this ongoing phase 1/2 study demonstrate that the novel BTK degrader BGB-16673 has a manageable safety profile with a low rate of discontinuation due to TEAEs
- BGB-16673 elicited clinical responses in heavily pretreated patients with B-cell malignancies, including those with BTK inhibitor-resistant disease or high-risk molecular features
  - The ORR was 57.4% in all patients, 71.4% (5/7) in patients with *BTK* mutation, and 56.0% (14/25) in patients with del(17p) or *TP53* mutation
  - Six patients (12.8%) achieved CR (MCL, n=3; DLBCL, FL, and MZL, n=1 each)
  - Median time to response was short (<3 months), which was consistent with results from the global parallel CaDAnCe-101 study[1]
- These data support further investigation of BGB-16673 in patients with B-cell malignancies

1. Seymour JF, et al. ASH 2023; Abstract 4401.

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