First Results From a Phase 1, First-in-Human Study of the Bruton Tyrosine Kinase Degrader BGB-16673 in Patients With Relapsed/Refractory B-Cell Malignancies

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Background

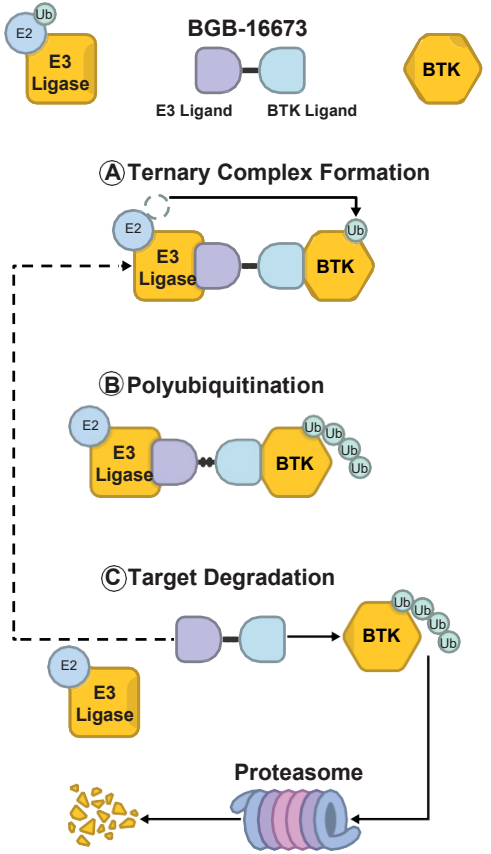
- BTK inhibitors have become a standard of care treatment for patients with CLL, Waldenström macroglobulinemia, MCL, and marginal zone lymphoma
- However, many patients experience disease progression in part due to resistance mutations within BTK that arise during treatment with both covalent or non-covalent BTK inhibitors[1,2]
- BGB-16673, a CDAC, is a bivalent molecule comprising a BTK-binding moiety + linker + E3 ligase binder; engagement of the drug with BTK activates the ubiquitination pathway, resulting in degradation of BTK
- In preclinical models, BGB-16673 degraded both wild-type BTK and known covalent and noncovalent BTK inhibitor–resistant mutant proteins such as V416L, M437R, T474I, C481S, C481F, C481Y, and L528W, leading to tumor regression[3,4]
- Here, we report the preliminary safety and efficacy results of the BGB-16673-101 study (NCT05006716) in patients with relapsed or refractory B-cell malignancies

1. Woyach JA, et al. *N Engl J Med.* 2014; 370:2286-2294; 2. Wang E, et al. *N Engl J Med.* 2022; 386:735-743; 3. Feng X, et al. EHA 2023. Abstract P1239;
4. Wang H, et al. EHA 2023. Abstract P1219.
BTK, Bruton tyrosine kinase; CDAC, chimeric degradation activating compound; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma.

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
- Has substantially reduced immunomodulatory drug activity; Aiolos and Ikaros are not significantly degraded



BTK, Bruton tyrosine kinase; CDAC, chimeric degradation activating compound.

BGB-16673-101 Study Design[a]

Key eligibility criteria

- Received ≥2 prior therapies (≥1 prior therapy for RT)
- Received a cBTKi if approved for their disease
- ECOG PS 0-2
- Adequate end-organ function
- No current or history of central nervous system involvement by B-cell malignancy

Key study objectives

- **Primary:** safety[c] and tolerability, define MTD and RP2D
- **Secondary:** characterize PK, pharmacodynamics, and preliminary antitumor activity[d]

Part 1: Monotherapy dose finding (concurrent enrollment)

Part 1a: Dose escalation[b]

Selected R/R B-cell malignancies
(MZL, FL, MCL, CLL/SLL, WM, DLBCL, RT)
n≤72

50 mg QD → 100 mg QD → 200 mg QD → 350 mg QD → 500 mg QD → 600 mg QD

Oral dosing

Part 1b: Safety expansion

Selected R/R B-cell malignancies
(MZL, MCL, CLL/SLL, WM)
n≤120

Up to 20 patients enrolled at doses that are cleared in part 1a: dose escalation and recommended for additional evaluation by the safety monitoring committee

Part 1c: Additional safety expansion

Selected R/R B-cell malignancies
(MZL, WM, RT, DLBCL, FL)
n≤40

After part 2 is opened, up to 40 patients enrolled in up to 3 dose levels as recommended by the safety monitoring committee

Determination of BGB-16673 RP2D

Part 2: Dose Expansion

Cohort 1: Post-BTK inhibitor, R/R CLL/SLL

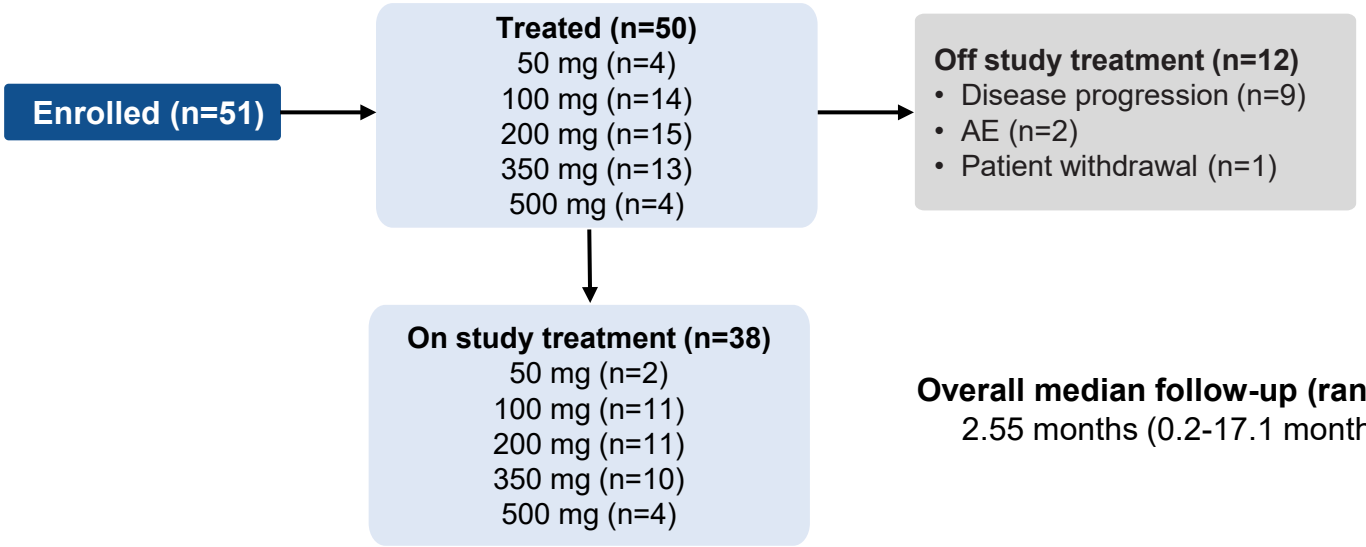
Cohort 2: Post-BTK inhibitor, R/R MCL

[a] Gray portions of the diagram are intended trial elements that have not yet commenced. [b] Bayesian optimal interval design with 6 dose levels (50-600 mg orally QD).
[c] Safety was assessed according to CTCAE v5.0 in all patients and iwCLL hematologic toxicity criteria in patients with CLL; DLTs were assessed during the first 4 weeks.
[d] Response was assessed per Lugano criteria for all patients except those with CLL (per iwCLL 2018 criteria) and WM (per IWWM-6 criteria)[1-3]

1. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3067; 2. Hallek M, et al. *Blood.* 2018;131:2745-2760; 3. Owen RG, et al. *Br J Haematol.* 2022; 160:171-176.

cBTKi, covalent Bruton tyrosine kinase inhibitor; RT, Richter transformation.

Patient Disposition[a]



Overall median follow-up (range):
2.55 months (0.2-17.1 months)

[a] Data for parts 1a and 1b were pooled for each dose level and histology. One patient was enrolled but had not yet received study treatment at the September 1, 2023 data cutoff date.

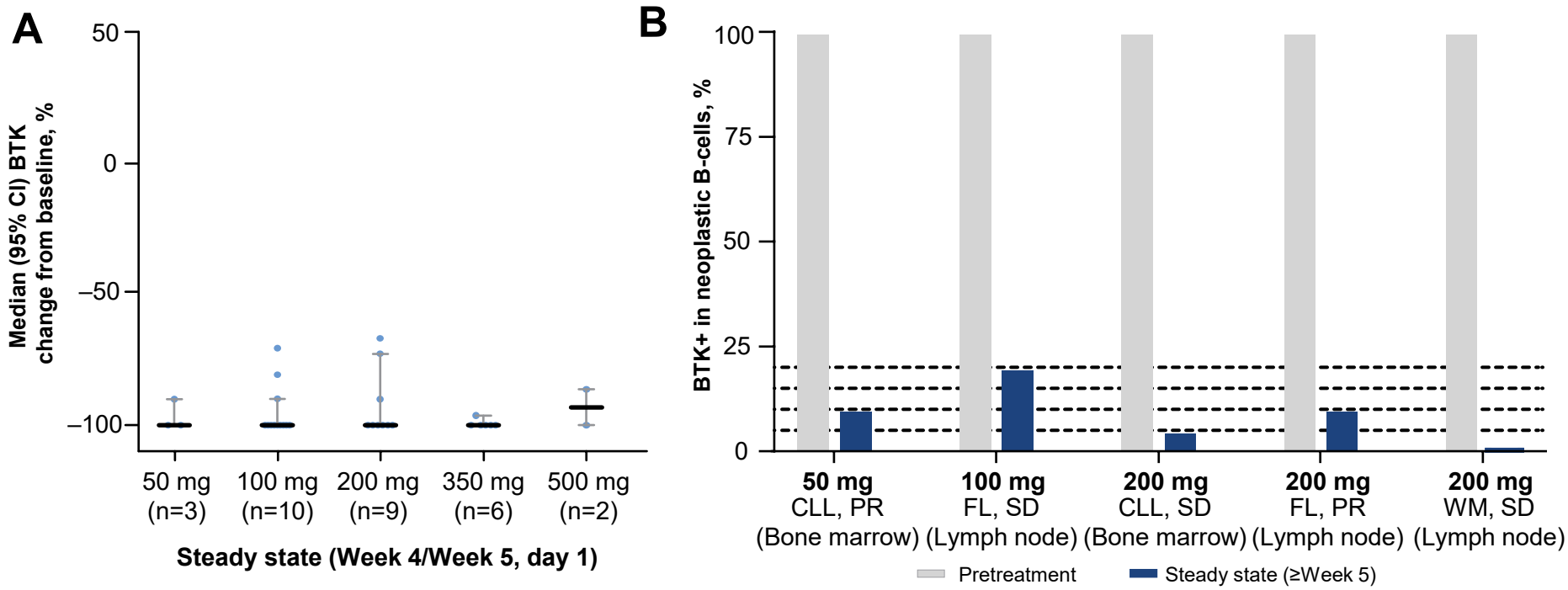
Demographic and Baseline Characteristics

Parameter	Total (N=50)
Age, median (range), years	70.5 (25-91)
Sex, n (%)	
Male	33 (66)
Female	17 (34)
ECOG performance status, n (%)	
0-1	47 (94)
2	3 (6)
Disease type, n (%)	
CLL/SLL	24 (48)
MCL	7 (14)
MZL	3 (6)
WM	6 (12)
DLBCL	2 (4)
FL	6 (12)
RT	2 (4)
Number of prior lines, median (range)	4 (2-10)
Prior covalent BTK inhibitor	40 (80)
Prior noncovalent BTK inhibitor	7 (14)
Discontinued BTK inhibitor due to PD	28 (56)
BCL2 inhibitor	28 (56)

Parameter	Total (N=50)
Mutation status, n/N (%)	
BTK mutation present	7/24 (29)
PLCG2 mutation present	2/24 (8)
BCL2 mutation present	12/27 (44)
CLL/SLL risk characteristics at study entry, n/N (%)	
Binet stage 3 at study entry	12/23 (52)
Unmutated IGHV locus	16/19 (84)[a]
del(17p)	8/24 (33)
TP53 mutation	10/23 (42)[b]
del(17p) or *TP53* mutation	11/23 (46)[b]
del(11q)	2/24 (8)
Complex karyotype (≥3 abnormalities)	8/20 (40)[c]

[a] Results missing for 5 patients. [b] Results missing for 1 patient. [c] Results missing for 4 patients.
BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; IGHV, immunoglobulin heavy chain variable region; *TP53*, tumor protein 53.

Reduction of BTK Protein Levels in A) Peripheral Blood and B) Tumor Tissue



[a] BTK protein levels were measured in whole blood lysates by ELISA. [b] Percentage of BTK-positive neoplastic B-cells were measured by immunohistochemistry in paired pretreatment and steady state tumor tissue collected from lymph nodes or bone marrow. Week 13 response data are shown.
BTK, Bruton tyrosine kinase; ELISA, enzyme-linked immunosorbent assay.

Overall Safety Summary

Patients, n (%)	50 mg (n=4)	100 mg (n=14)	200 mg (n=15)	350 mg (n=13)	500 mg (n=4)	All (N=50)
Any TEAE	4 (100)	13 (93)	13 (87)	12 (92)	4 (100)	46 (92)
Grade 3 or higher	3 (75)	4 (29)	6 (40)	5 (38)	1 (25)	19 (38)
Serious	1 (25)	4 (29)	5 (33)	4 (31)	0	14 (28)
Leading to death[a]	0	0	2 (13)	0	0	2 (4)
Leading to treatment discontinuation	0	0	1 (7)	2 (15)	0	3 (6)
Leading to treatment modification	1 (25)	4 (29)	4 (27)	2 (15)	0	11 (22)
Dose interruption	1 (25)	4 (29)	4 (27)	2 (15)	0	11 (22)
Dose reduction[b]	1 (25)	1 (7)	0	0	0	2 (4)
DLT[c]	0	0	1 (7)	0	0	1 (2)

[a] 1) Septic shock (200 mg) in the context of progressive disease; 2) pneumonia (200 mg) in the context of progressive disease. [b] 1) Hematuria (50 mg) in the context of subsequently identified recurrent urothelial carcinoma; 2) arthralgia (100 mg) in the context of a previous history of BTK inhibitor–associated arthralgia. [c] Grade 3 maculopapular rash of face and legs (200 mg) at end of DLT reporting period. After 5-day dose hold and following improvement of rash, treatment was restarted and patient remains on the assigned dose.
BTK, Bruton tyrosine kinase.

TEAEs in ≥10% of All Patients or ≥3% for Grade 3 or Higher

Patients, n (%)	All (N=50)	
	All Gr	Gr ≥3
Contusion	15 (30)	0
Diarrhea	12 (24)	0
Fatigue	10 (20)	0
Amylase increased[a]	8 (16)	0
Neutropenia/neutrophil count decreased	8 (16)	6 (12)
Lipase increased[a]	7 (14)	2 (4)
Pyrexia	7 (14)	0
Cough	6 (12)	0
Headache	5 (10)	0
Thrombocytopenia/platelet count decreased	5 (10)	2 (4)
Pneumonia	3 (6)	3 (6)
COVID-19 pneumonia	2 (4)	2 (4)
Grouped TEAEs of interest		
Any bleeding	21 (42)	2 (4)[b]
Any infection[c]	20 (40)	8 (16)
Atrial fibrillation/flutter	0	0
Hypertension	0	0

[a] Transient laboratory-only findings; no associated gastrointestinal symptoms or dose modifications. [b] 1) Hematuria (50 mg) in the context of subsequently identified recurrent urothelial carcinoma; 2) subdural hemorrhage (350 mg), resolving (related). [c] Includes 4 upper respiratory tract infection, 3 pneumonia, 3 urinary tract infection, 2 COVID-19 or COVID-19 pneumonia, 2 cellulitis, and 2 hordeolum (stye).
Gr, grade.

Responses by Dose in Evaluable Patients

	50 mg (n=4)	100 mg (n=10)	200 mg (n=9)	350 mg (n=4)	500 mg (n=1)	All Doses (N=28)
Best overall response, n (%)						
CR	1 (25)	0	0	0	0	1 (4)
PR	1 (25)	4 (40)	7 (78)	0	1 (100)	13 (46)
PR-L	0	0	1 (11)	0	0	1 (4)
MR	0	1 (10)	0	0	0	1 (4)
SD	0	3 (30)	1 (11)	1 (25)	0	5 (18)
PD	2 (50)	2 (20)	0	1 (25)	0	5 (18)
Discontinued prior to first assessment	0	0	0	2 (50)	0	2 (7)
Disease control rate, n (%)[a]	**2 (50)**	**8 (80)**	**9 (100)**	**1 (25)**	**1 (100)**	**21 (75)**
ORR, n (%)[b]	**2 (50)**	**5 (50)**	**8 (89)**	**0**	**1 (100)**	**16 (57)**
Median time to first response, months[c]	2.60	0.95	2.81	–	2.83	2.76

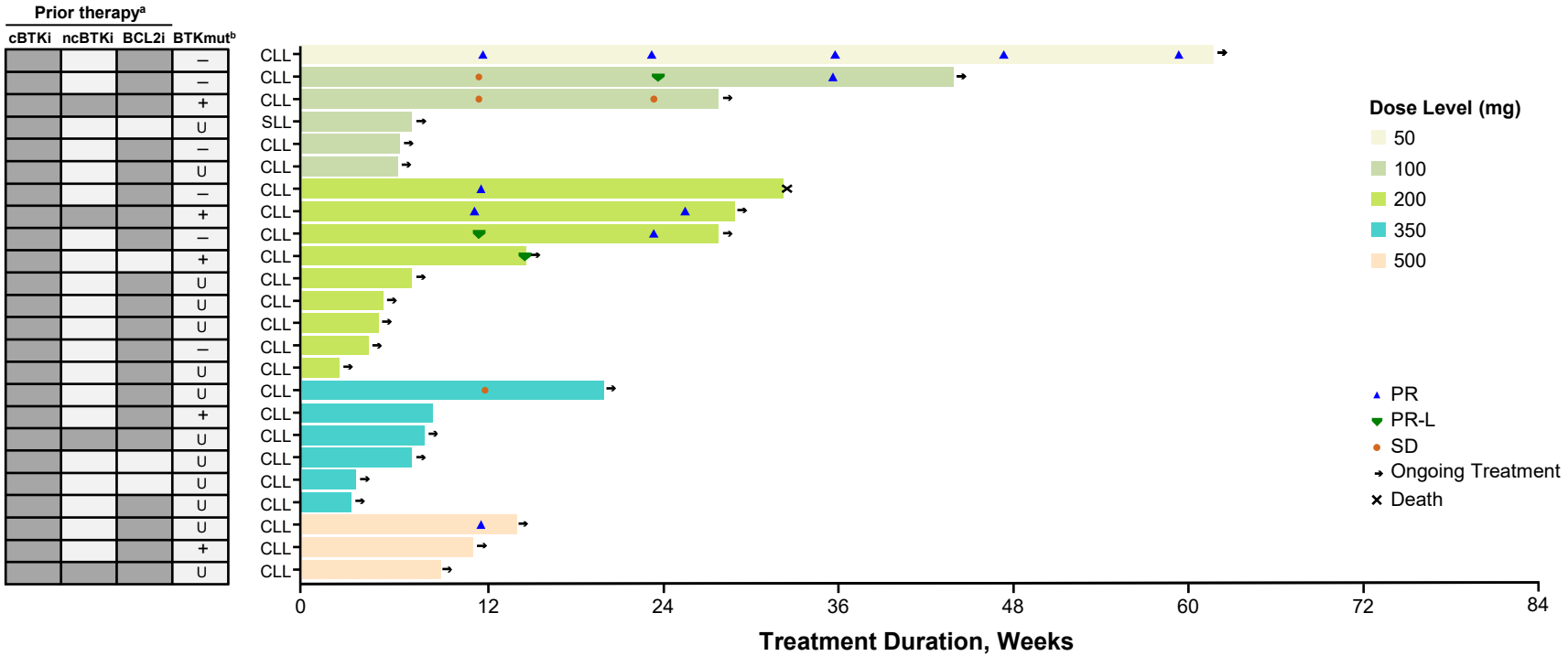
[a] Proportion of patients with a best overall response of SD or higher. [b] Proportion of patients who achieved a best overall response better than SD. [c] Time to first qualifying response in patients with a best overall response better than SD.

Responses by Histology in Evaluable Patients

	CLL/SLL (n=10)	MCL/MZL/WM/ FL (n=16)	DLBCL/RT (n=2)	All (n=28)
Best overall response, n (%)				
CR	0	1 (6)	0	1 (4)
PR	6 (60)	7 (44)	0	13 (46)
PR-L	1 (10)	N/A	N/A	1 (4)
MR	N/A	1 (6)	0	1 (4)
SD	2 (20)	3 (19)	0	5 (18)
PD	0	3 (19)	2 (100)	5 (18)
Discontinued prior to first assessment	1 (10)	1 (6)	0	2 (7)
Disease control rate, n (%)[a]	**9 (90)**	**12 (75)**	**0**	**21 (75)**
ORR, n (%)[b]	**7 (70)**	**9 (56)[d]**	**0**	**16 (57)**
Median time to first response, months[c]	2.83	2.33	N/A	2.76

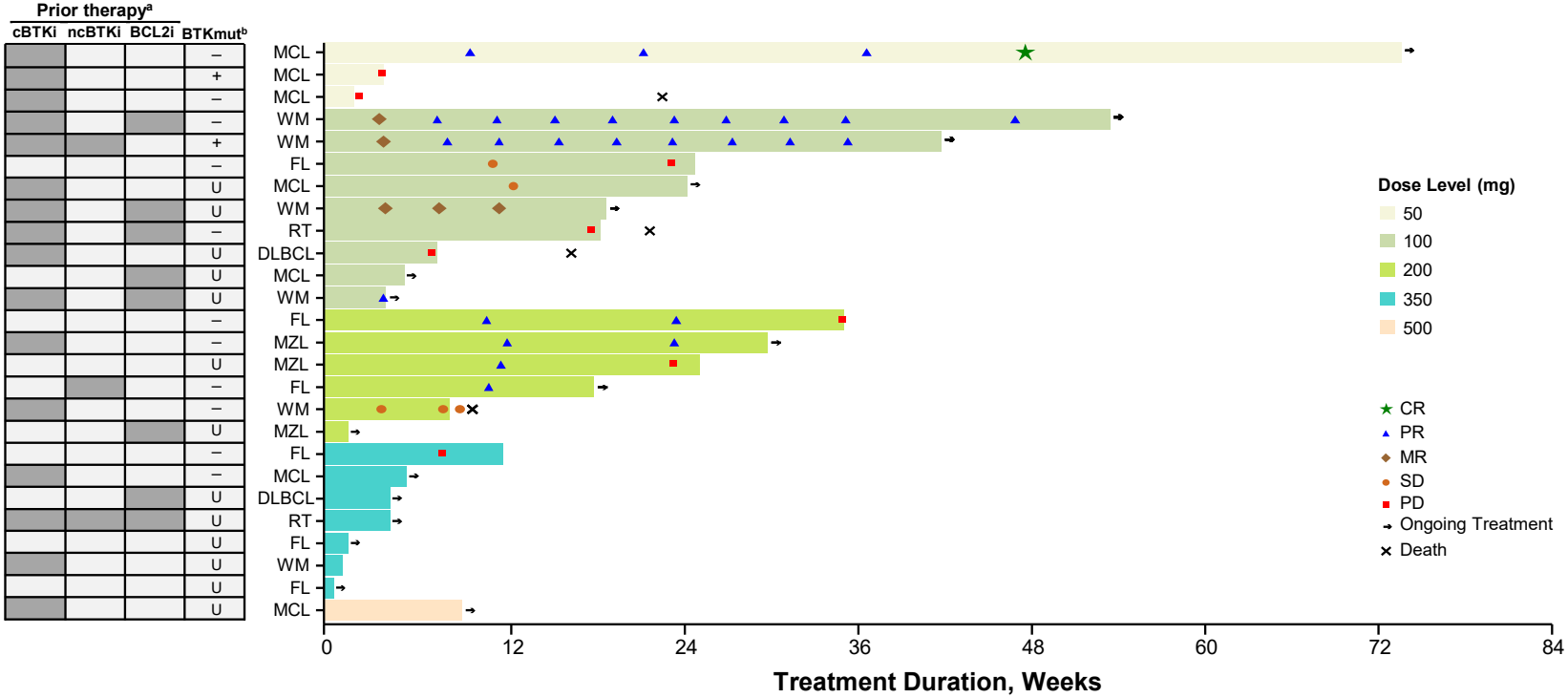
[a] Proportion of patients with a best overall response of SD or higher. [b] Proportion of patients who achieved a best overall response better than SD. [c] Time to first qualifying response in patients with a best overall response better than SD. [d] CR=1 MCL; PR=3 WM, 2 MZL, 2 FL; MR=1 WM.
RT, Richter transformation.

Treatment Duration and Response Assessment in Patients with CLL/SLL



[a] Gray shading = patient had the indicated prior therapy. [b] BTK mutation status was classified as present (+), absent (-), or unknown (U).
BCL2i, B-cell lymphoma 2 inhibitor; BTK, Bruton tyrosine kinase; cBTKi, covalent BTK inhibitor; mut, mutation; ncBTKi, noncovalent BTK inhibitor.

Response Assessment in Patients with Other Indolent B-cell Lymphomas



[a] Gray shading = patient had the indicated prior therapy. [b] BTK mutation status was classified as present (+), absent (-), or unknown (U).
BCL2i, B-cell lymphoma 2 inhibitor; BTK, Bruton tyrosine kinase; cBTKi, covalent BTK inhibitor; mut, mutation; ncBTKi, noncovalent BTK inhibitor.

Conclusions

- Preliminary results from this ongoing, first-in-human study of the novel BTK degrader BGB-16673 demonstrate meaningful clinical responses with a short time to response in heavily pretreated patients with a range of B-cell malignancies
  - In a high-risk, heavily pretreated population of patients with CLL/SLL all treated with cBTK inhibitors, the ORR was 70%
- The safety profile of BGB-16673 appears tolerable to date with a single DLT (rash) reported and the study continues
  - Discontinuations due to TEAEs were low (2 of 50 patients)
  - No atrial fibrillation or hypertension has been reported so far
- Substantial reductions in BTK protein levels in peripheral blood and tumor tissue were also observed, demonstrating proof-of-concept of a strong, on-target effect
- Taken together, these data support further examination of the clinical activity of BGB-16673 across several B-cell malignancies; phase 2 dose expansions are planned within this study for patients with CLL/SLL and MCL

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Current Open and Selected Sites for Patient Enrollment