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CaDAnCe-101

BGB-16673, a BTK Degrader, in Patients With R/R CLL/SLL: Preliminary Phase 1 Results From CaDAnCe-101

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Disclosures for Talha Munir

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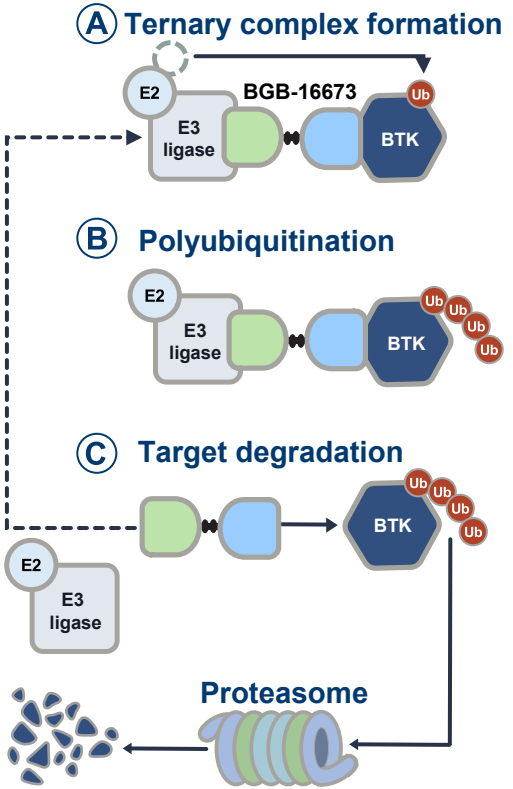
BGB-16673: A Chimeric Degradation Activating Compound (CDAC)

- Many patients with CLL/SLL experience disease progression with BTK inhibitors, which can be caused by resistance mutations in BTK[1-3]
- BGB-16673 is a potential first-in-class protein degrader that blocks BTK signaling by tagging BTK for degradation through the cell's proteasome pathway[4]
- In preclinical models, BGB-16673 degraded both wild-type and mutant BTK resistant to cBTK (C481S, C481F, C481Y, L528W, T474I) and ncBTK inhibitors (V416L, M437R, T474I, L528W), leading to tumor suppression[4,5]
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue[6]
- We present updated safety and efficacy results in patients with R/R CLL/SLL and preliminary efficacy results in patients with R/R RT from phase 1 of CaDAnCe-101



cBTK, covalent BTK; ncBTK, noncovalent BTK; RT, Richter transformation; ub, ubiquitin.

1. Moreno C. *Hematol Am Soc Hematol Educ Program*. 2020;2020:33-40; 2. Woyach JA, et al. *N Engl J Med*. 2014;370:2286-2294; 3. Wang E, et al. *N Engl J Med*. 2022;386:735-743; 4. Feng X, et al. EHA 2023. Abstract P1239; 5. Wang H, et al. EHA 2023. Abstract P1219; 6. Seymour JF, et al. ASH 2023; Abstract 4401.

CaDAnCe-101: Phase 1/2, Open-Label, Dose-Escalation/Expansion Study in R/R B-Cell Malignancies

CaDAnCe-101 (BGB-16673-101, NCT05006716)

Key eligibility criteria for CLL/SLL

- Meets iwCLL 2018 criteria for treatment
- ≥2 prior therapies, including cBTKi if approved for disease
- ECOG PS 0-2 & adequate end-organ function

Key study objectives for part 1

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

Part 1: Monotherapy dose finding[a]

Part 1a: Dose escalation
Selected R/R B-cell malignancies
(MZL, FL, MCL, **CLL/SLL**, WM, DLBCL, RT)
n≤72
Oral, QD, 28-day cycle[b]
Doses: 50 mg, 100 mg, 200 mg, 350 mg, 500 mg, 600 mg

Part 1b: Safety expansion
Selected R/R B-cell malignancies
(MZL, MCL, **CLL/SLL**, WM)
n≤120

Part 1c: Additional safety expansion
Selected R/R B-cell malignancies
(MZL, WM, RT, DLBCL, FL)
n≤100

Part 1d: Additional safety expansion
R/R CLL/SLL
n≤30

Part 1e: Additional safety expansion
Selected R/R B-cell malignancies (Japan only)
(MZL, FL, MCL, CLL/SLL, WM)
n=6-9

Part 1f: Monotherapy safety expansion
Selected BTK inhibitor–naive B-cell malignancies
(MZL, MCL, CLL/SLL, WM, RT)
n≤40

Determination of BGB-16673 RDFE

Phase 2

- **Cohort 1:** Post BTK inhibitor, R/R CLL/SLL
- **Cohort 2:** Post BTK inhibitor, R/R MCL
- **Cohort 3:** Post BTK inhibitor, R/R WM
- **Cohort 4:** Post BTK inhibitor, R/R MZL
- **Cohort 5:** R/R FL
- **Cohort 6:** R/R non-GCB DLBCL
- **Cohort 7:** Post BTK inhibitor, R/R RT

[a] Data from gray portions of the figure are not included in this presentation. [b] Treatment was administered until progression, intolerance, or meeting other criteria for treatment discontinuation. [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 of part 1a. [d] Response was assessed per iwCLL 2018 criteria after 12 weeks in patients with CLL; response was assessed per Lugano criteria after 12 weeks in patients with RT.
GCB, germinal center B cell; RT, Richter transformation.

Baseline Patient Characteristics

Heavily pretreated, with high-risk CLL features

	Total (N=60)
Age, median (range), years	70 (50-91)
Male, n (%)	39 (65.0)
ECOG PS, n (%)	
0	34 (56.7)
1	25 (41.7)
2	1 (1.7)
CLL/SLL risk characteristics at study entry, n/N with known status (%)	
Binet stage C	27/56 (48.2)
Unmutated IGHV	38/46 (82.6)
del(17p) and/or *TP53* mutation	40/60 (66.7)
Complex karyotype (≥3 abnormalities)	19/38 (50.0)

	Total (N=60)
Mutation status, n/N (%)	
BTK mutation present	18/54 (33.3)
PLCG2 mutation present	8/54 (14.8)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	43 (71.7)
cBTK inhibitor	56 (93.3)
ncBTK inhibitor	13 (21.7)
BCL2 inhibitor	50 (83.3)
cBTK + BCL2 inhibitors	38 (63.3)
cBTK + ncBTK + BCL2 inhibitors	12 (20.0)
Discontinued prior BTK inhibitor due to PD, n/N (%)[a]	50/56 (89.3)

Data cutoff: September 2, 2024.

[a] Remaining 6 patients discontinued prior BTK inhibitor due to toxicity (n=3), treatment completion (2), and other (n=1).

cBTK, covalent BTK; ncBTK, noncovalent BTK.

Overall Safety Summary

No treatment-related TEAEs leading to death

- One DLT[a] at 200-mg dose (grade 3 maculopapular rash; patient continued on treatment after a 5-day hold)

Patients, n (%)	Total (N=60)
Any TEAE	56 (93.3)
Any treatment-related	41 (68.3)
Grade ≥3	33 (55.0)
Treatment-related grade ≥3	16 (26.7)
Serious	27 (45.0)
Treatment-related serious	6 (10.0)
Leading to death	3 (5.0)
Treatment-related leading to death	0
Leading to treatment discontinuation	7 (11.7)
Treatment-related leading to treatment discontinuation	2 (3.3)

Median follow-up for safety-evaluable patients: 10.2 months (range, 0.3-26.4+).

[a] DLTs were only assessed during the first 4 weeks of part 1a.

Safety Summary and All-Grade TEAEs in ≥10% of All Patients

- No atrial fibrillation
- No pancreatitis
- Major hemorrhage[b]: 3.3% (n=2; grade 1 subarachnoid hemorrhage [n=1] and grade 3 subdural hemorrhage [n=1])
- Febrile neutropenia: 1.7% (n=1; in the context of COVID-19 pneumonia and norovirus diarrhea)

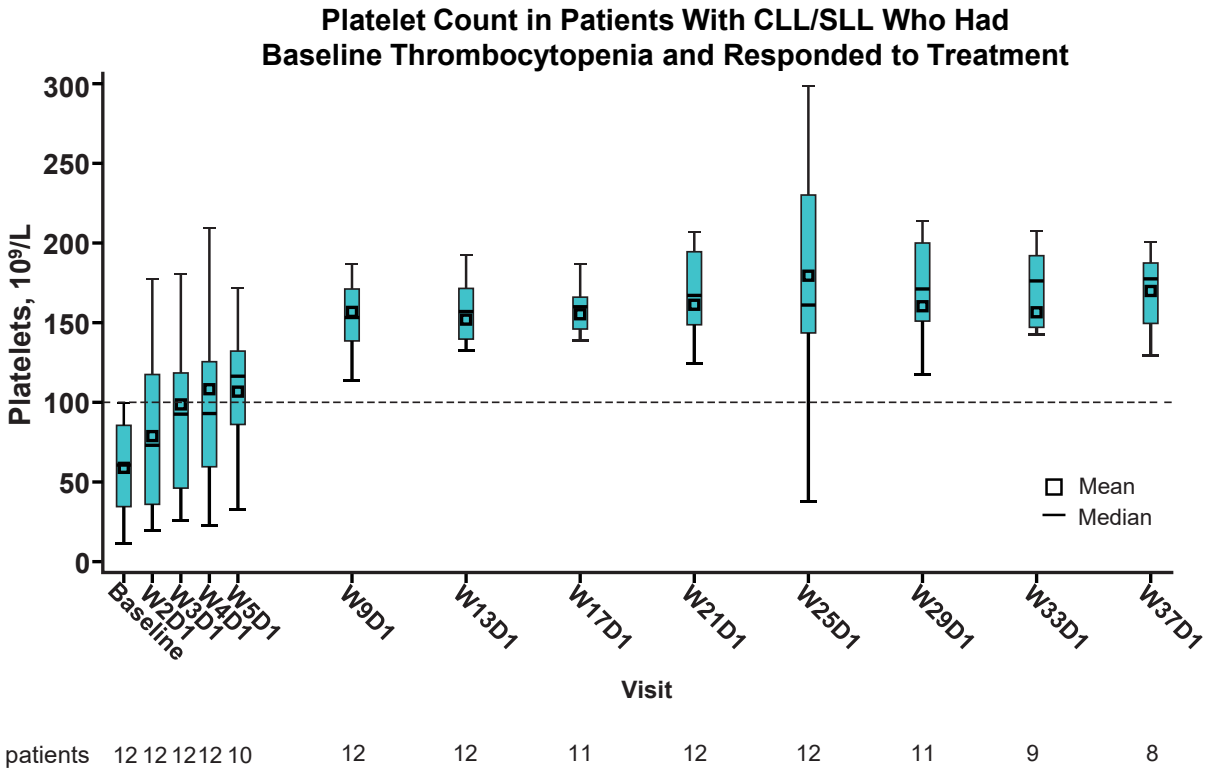
	Total (N=60)	
Patients, n (%)	All Grade	Grade ≥3
Fatigue	18 (30.0)	1 (1.7)
Contusion (bruising)	17 (28.3)	0
Neutropenia[c]	15 (25.0)	13 (21.7)
Diarrhea	14 (23.3)	1 (1.7)
Anemia	11 (18.3)	0
Lipase increased[a]	10 (16.7)	2 (3.3)
Cough	9 (15.0)	0
Pneumonia	8 (13.3)	5 (8.3)
Pyrexia	8 (13.3)	0
Arthralgia	7 (11.7)	0
COVID-19	7 (11.7)	0
Dyspnea	7 (11.7)	0
Peripheral edema	7 (11.7)	0
Thrombocytopenia[d]	7 (11.7)	2 (3.3)
Amylase increased[a]	6 (10.0)	0
Nausea	6 (10.0)	0
Sinusitis	6 (10.0)	0

Median follow-up: 10.2 months (range, 0.3-26.4+).

[a] All events were lab findings and were transient, mostly occurring during the first 1-3 cycles of treatment, with no clinical pancreatitis. [b] Grade ≥3, serious, or any central nervous system bleeding. [c] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [d] Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

Rapid and Significant Cytopenia Improvement in Patients With Treatment Response

- Median neutrophil count improved from 1.18 × 10^9/L at baseline to 2.76 × 10^9/L at W9D1[a]
- Median hemoglobin level improved from 9.9 g/dL at baseline to 11.0 g/dL at W13D1[b]
- Median platelet count improved from 60.5 × 10^9/L at baseline to 153.0 × 10^9/L at W9D1[c]



[a] For n=10 patients based on 1.5 × 10^9/L cutoff. [b] For n=17 patients based on 11.0 g/dL cutoff. [c] For n=12 patients based on 100 × 10^9/L cutoff.

Overall Response Rate

Significant Responses, Particularly at 200-mg Dose Level

	50 mg (n=1)	100 mg (n=5)	200 mg (n=16)	350 mg (n=15)	500 mg (n=12)	Total[a] (N=49)
Best overall response, n (%)						
CR/CRi	0	1 (20.0)	1 (6.3)	0	0	**2 (4.1)**
PR[b]	1 (100)	3 (60.0)	12 (75.0)	10 (66.7)	7 (58.3)	33 (67.3)
PR-L	0	0	2 (12.5)	0	1 (8.3)	3 (6.1)
SD	0	1 (20.0)	0	1 (6.7)	4 (33.3)	6 (12.2)
PD	0	0	1 (6.3)	1 (6.7)	0	2 (4.1)
Discontinued prior to first assessment	0	0	0	3 (20.0)	0	3 (6.1)
ORR, n (%)[c]	1 (100)	4 (80.0)	**15 (93.8)**	10 (66.7)	8 (66.7)	**38 (77.6)**
Disease control rate, n (%)[d]	1 (100)	5 (100)	15 (93.8)	11 (73.3)	12 (100)	44 (89.8)
Time to first response, median (range), months[e]	2.9 (2.9-2.9)	4.2 (2.8-6.2)	2.9 (2.6-8.3)	2.8 (2.6-8.3)	2.8 (2.6-8.3)	2.8 (2.6-8.3)
Time to best response, median (range), months	2.9 (2.9-2.9)	5.6 (2.8-11.1)	3.4 (2.6-13.8)	5.6 (2.6-8.3)	4.2 (2.6-8.6)	3.6 (2.6-13.8)
Duration of exposure, median (range), months	26.4 (26.4-26.4)	13.8 (13.6-18.6)	10.6 (2.9-18.9)	10.3 (0.2-16.8)	9.3 (6.8-15.4)	10.4 (0.2-26.4)

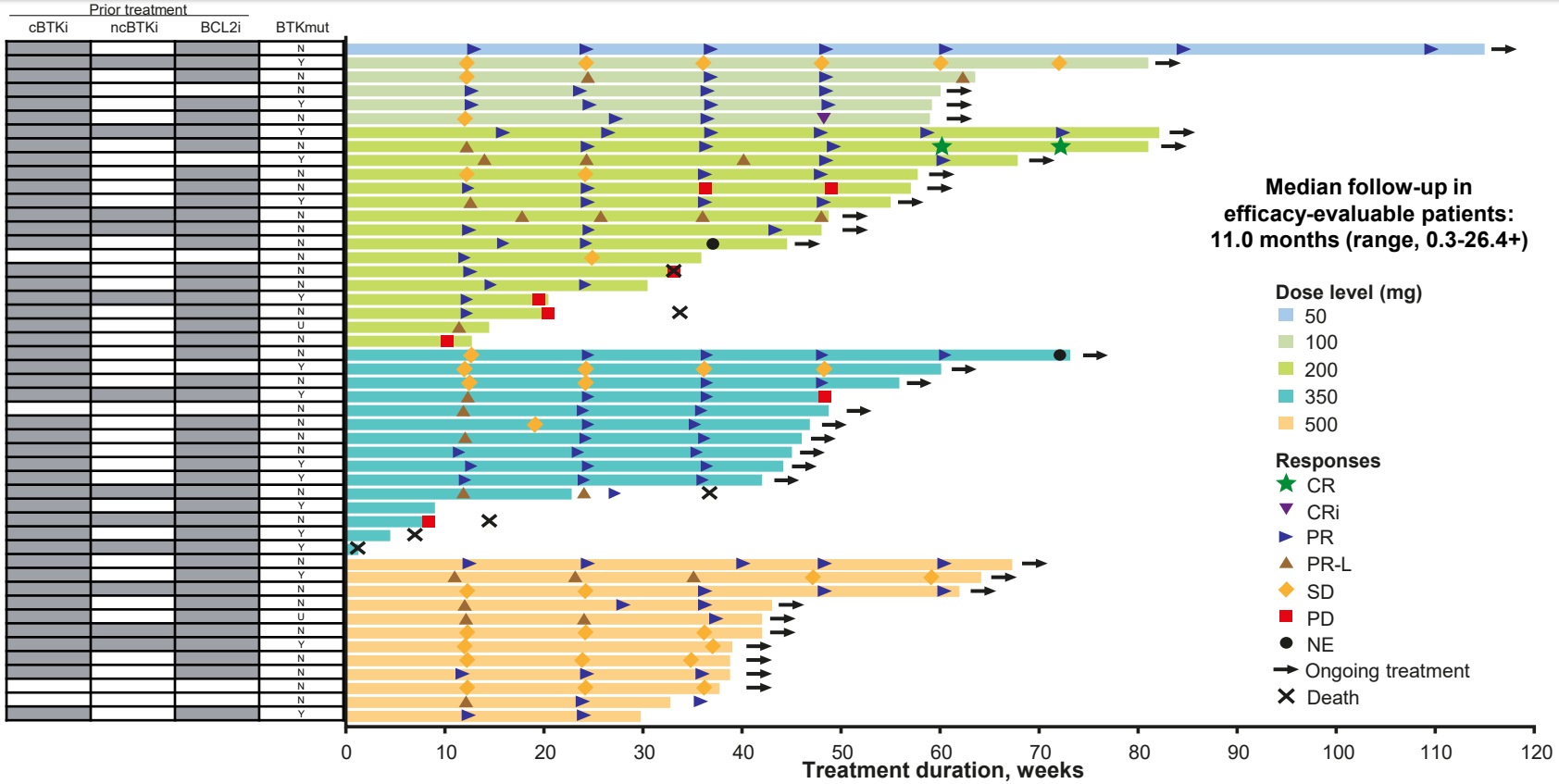
[a] Efficacy-evaluable population. [b] Out of 33 patients with PR, 8 achieved all nodes normalized. [c] Includes best overall response of PR-L or better. [d] Includes best overall response of SD or better. [e] In patients with a best overall response of PR-L or better.
CRi, complete response with incomplete marrow recovery; PR-L, partial response with lymphocytosis.

High Overall Response Rates in All Biologic Subsets

Characteristic, n/N with known status (%)	Total (N=49)[a]
Double exposure (previously received cBTKi + BCL2i)	26/30 (86.7)
Triple exposure (previously received cBTKi + ncBTKi + BCL2i)	7/12 (58.3)
del(17p) and/or *TP53* mutation	23/31 (74.2)
Complex karyotype	11/15 (73.3)
***BTK* mutations**	10/16 (62.5)
***PLCG2* mutations**	4/6 (66.7)

[a] Efficacy-evaluable population.
BCL2i, BCL2 inhibitor; cBTKi, covalent BTK inhibitor; ncBTKi, non-covalent BTK inhibitor.

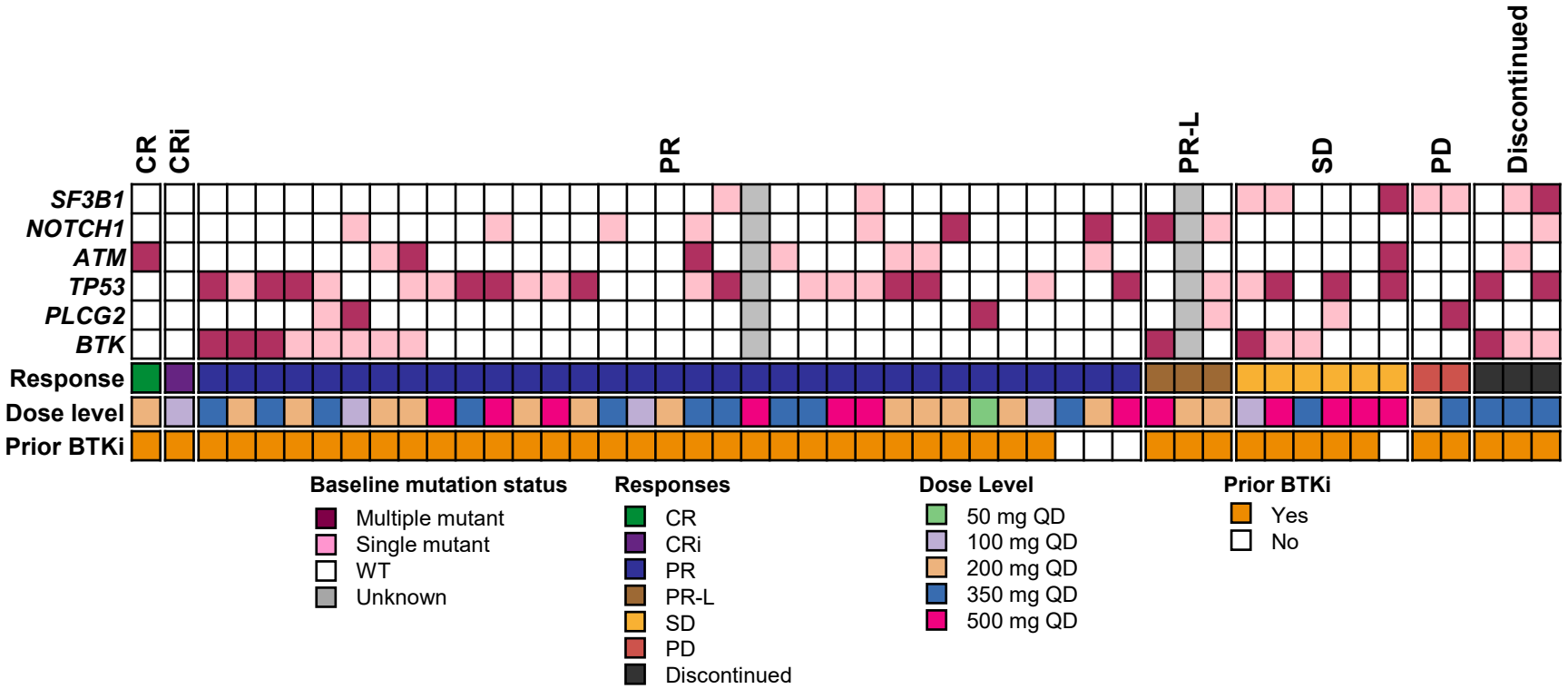
Treatment Duration and Response



Data cutoff: September 2, 2024. Efficacy-evaluable patients. First response assessment after 12 weeks.

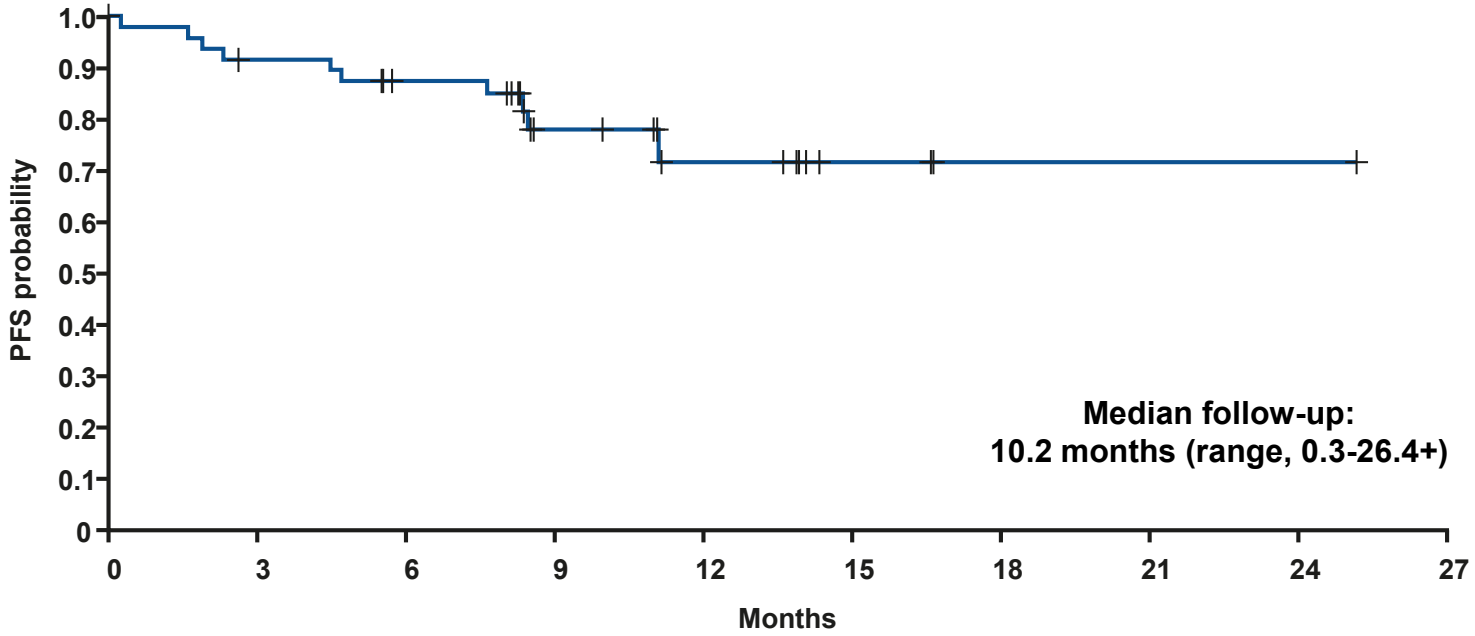
Responses Occurred Regardless of Specific Mutations

Best Overall Response vs. Baseline Mutation



BTKi, Bruton tyrosine kinase inhibitor; CRi, complete response with incomplete marrow recovery; PR-L, partial response with lymphocytosis; WT, wild type.

Progression-Free Survival

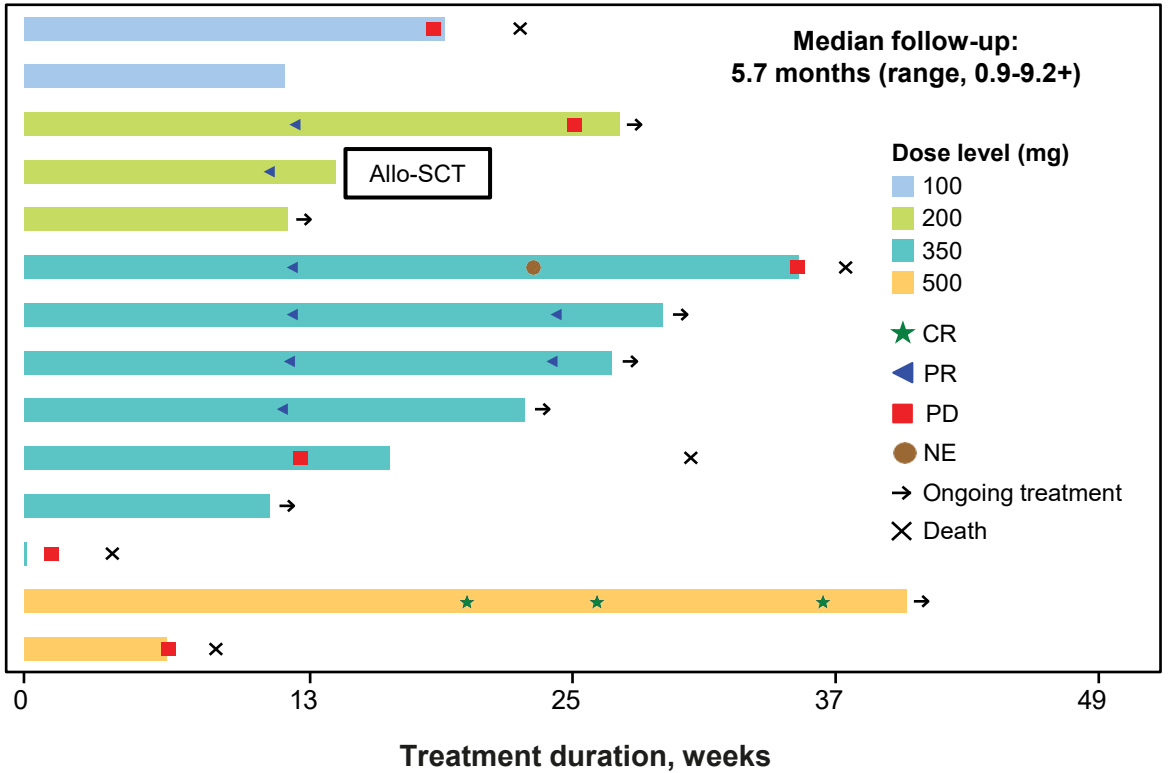


No. at risk:	60	43	37	20	10	4	1	1	1	0

Data cutoff: September 2, 2024.

Promising Activity Also Seen in Patients With Richter Transformation

- Safety-evaluable patients, n=14; efficacy-evaluable patients, n=12
- Median age (range): 64 years (47-80 years)
- Median prior number of therapies for RT (range): 2 (1-9)
- All patients previously received a cBTKi; 12/14 had anthracyclines
- ORR: 58.3% (7/12), **CR: 8.3% (1/12)**
- 5 of 7 (71.4%) patients with response on treatment for >6 months



Data cutoff: September 2, 2024.
cBTKi, covalent BTK inhibitor; NE, not evaluable.

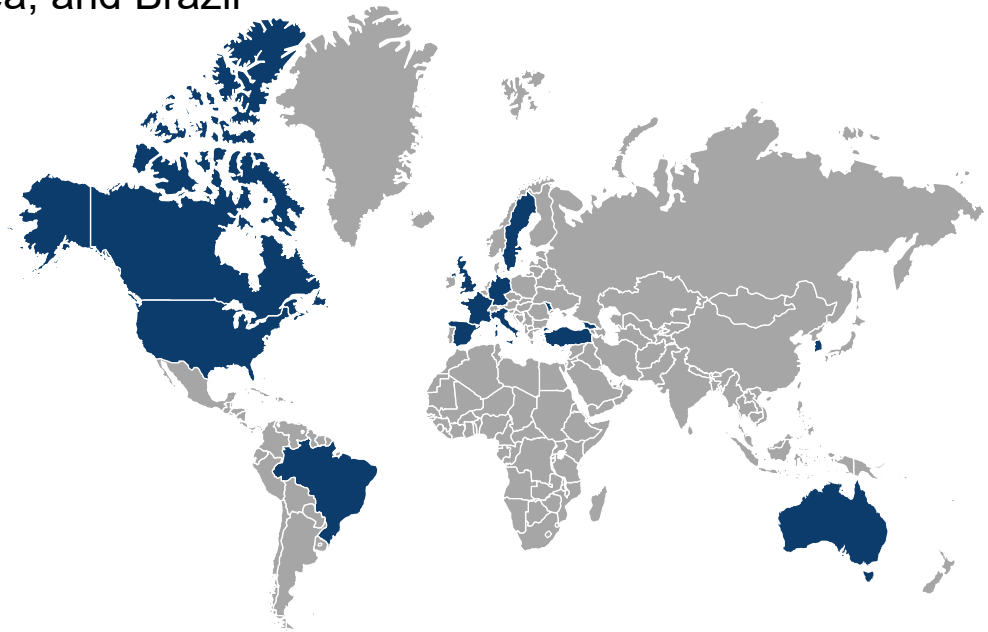
Conclusions

CaDAnCe-101

- In phase 1 of CaDAnCe-101, the novel BTK degrader BGB-16673 was safe and well tolerated in this heavily pretreated population of patients with R/R CLL/SLL
  - One DLT; MTD not reached
  - No atrial fibrillation
- Significant antitumor activity, including in patients with BTK inhibitor–resistant mutations and those previously exposed to cBTK, ncBTK, and BCL2 inhibitors
  - **ORR 77.6% (38/49) and CR/CRi 4.1% (2/49); ORR 93.8% at 200 mg**
  - Median time to first response: 2.8 months
  - Deepening of response observed over time (median 11.0-month follow-up)
- Promising activity in RT: ORR: 58.3% (7/12), **CR: 8.3% (1/12)**
- A phase 2 cohort of patients with CLL/SLL exposed to both a BTK inhibitor and BCL2 inhibitor is enrolling

CaDAnCe-101 Study Sites (Recruiting)

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



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