Preliminary Efficacy and Safety of the Bruton Tyrosine Kinase Degrader BGB-16673 in Patients With Relapsed or Refractory CLL/SLL: Results From the Phase 1 BGB-16673-101 Study

Ricardo D. Parrondo,[1] Meghan C. Thompson,[2] Anna Maria Frustaci,[3] John N. Allan,[4] Paolo Ghia,[5,6] Igori Vinogradov,[7] Constantine S. Tam,[8] Judith Trotman,[9] Michael Choi,[10] Xiangmei Chen,[11] Kunthel By,[12] Shannon Fabre,[12] Jason C. Paik,[12] Amit Agarwal,[12] John F. Seymour[13]

[1]Mayo Clinic - Jacksonville, Jacksonville, FL, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [4]Weill Cornell Medicine, New York, NY, USA; [5]Università Vita-Salute San Raffaele, Milano, Italy; [6]IRCCS Ospedale San Raffaele, Milano, Italy; [7]The Institute of Oncology, ARENSIA EXPLORATORY Medicine, Düsseldorf, Germany; [8]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [9]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [10]Moores Cancer Center, University of California San Diego, La Jolla, CA, USA; [11]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [12]BeiGene USA, Inc, San Mateo, CA, USA; [13]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and University of Melbourne, Melbourne, VIC, Australia

CaDAnCe-101

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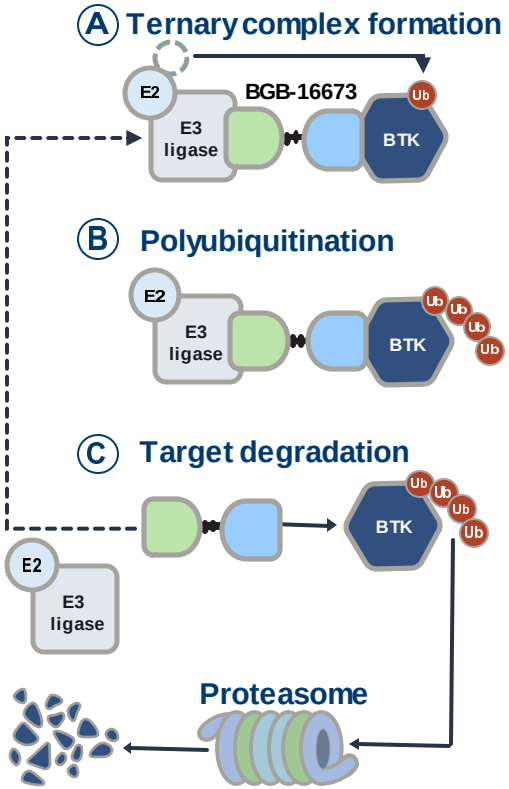
Disclosures

- **Ricardo D. Parrondo**: Bristol Myers Squibb, GSK (Research funding); Sanofi Aventis (Honoraria)

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

- Many patients with CLL/SLL experience disease progression after BTK inhibitors[1-3]
- BGB-16673, a CDAC, is a bivalent molecule comprising a BTK-binding moiety + linker + E3 ligase binder that induces BTK degradation via polyubiquitination[4]
- In preclinical models, BGB-16673 degraded both wild-type and mutant BTK resistant to covalent and noncovalent BTK inhibitors,[a] leading to tumor suppression[4,5]
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue in the first-in-human study[6]
- Here, the updated safety and efficacy results are presented from patients with R/R CLL/SLL in the ongoing CaDAnCe-101 study



[a] Covalent BTK inhibitor–resistant mutations including C481S, C481F, C481Y, L528W, and T474I; non-covalent BTK inhibitor–resistant mutations including V416L, M437R, T474I, and L528W. CDAC, chimeric degradation activating compound; ub, ubiquitin.

1. Tam CS, et al. *Blood Cancer J*. 2023;13(1):141-413; 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.

Study Design

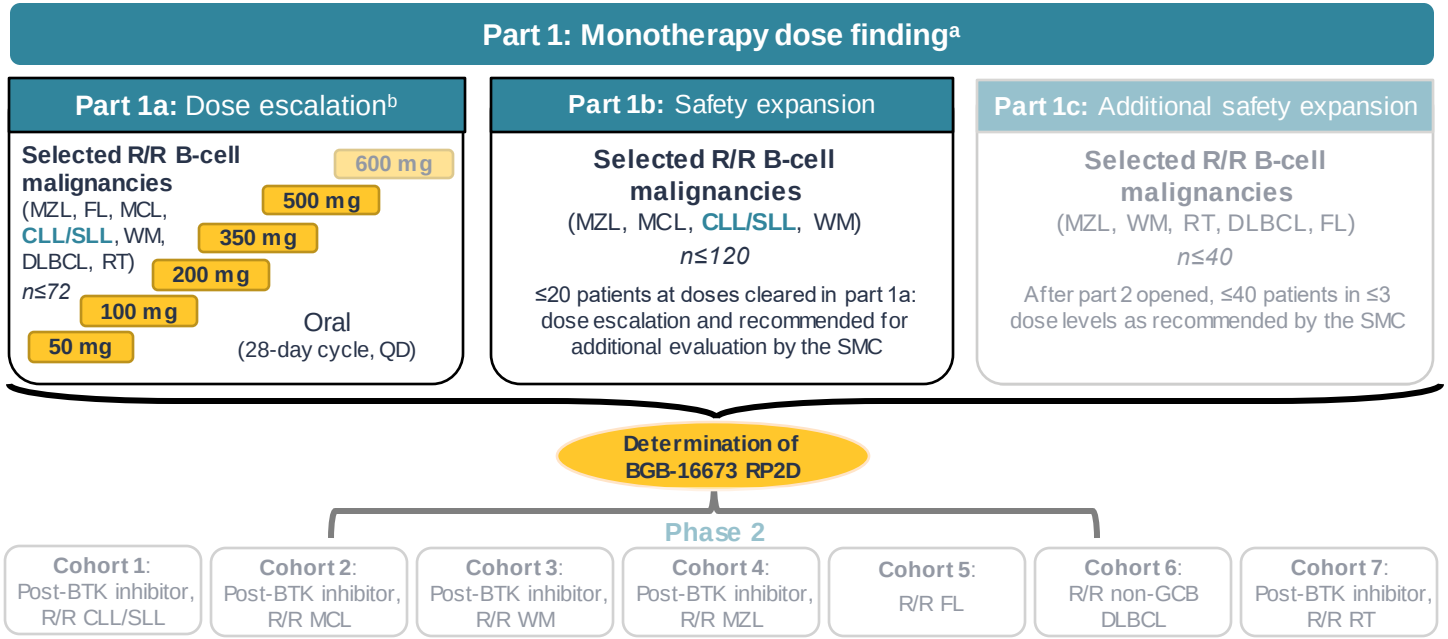
- CaDAnCe-101 (BGB-16673-101, NCT05006716) is a phase 1/2, open-label, dose-escalation and dose-expansion study evaluating BGB-16673 in adults with R/R B-cell malignancies

Key eligibility criteria for CLL/SLL

- Meets iw CLL 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

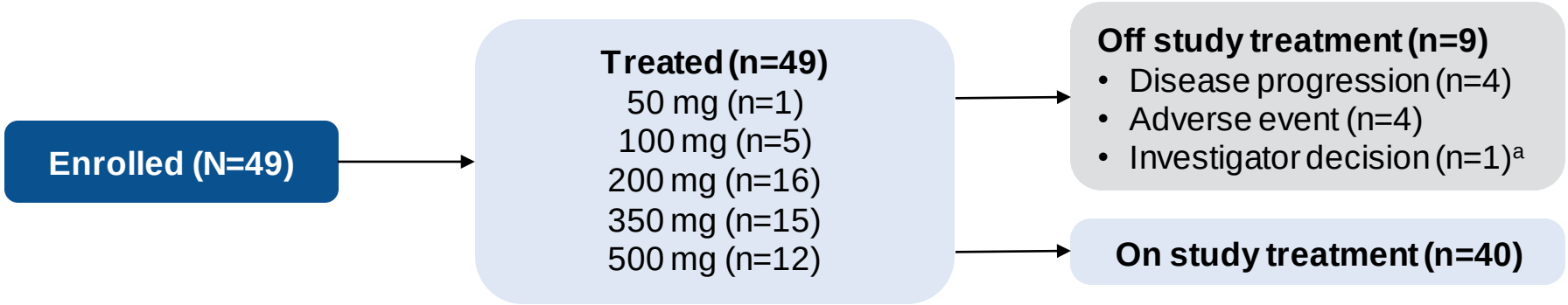
- **Primary:** safety[c] and tolerability, MTD, and RP2D
- **Secondary:** PK, PD, and preliminary antitumor activity[d]



[a] Data from grey portions of figure are not included in this presentation. [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 iwCLL 2018 criteria after 12 weeks for patients with CLL.[1]
GCB, germinal center B-cell; RT, Richter transformation. 1. Hallek M, et al. *Blood.* 2018;131:2745-2760.

Patient Disposition

- As of February 14, 2024, 49 patients with R/R CLL/SLL enrolled in Part 1A/1B and received BGB-16673
- Forty patients (82%) remained on treatment



Median follow-up (range):
4.60 months (0.3-19.8)

[a] Patient had ongoing low-grade arthralgia that did not otherwise meet the criteria for discontinuation.

Patient Characteristics

- Patients had a median of 4 (range, 2-10) prior lines of therapy
- Of patients with available data, high-risk characteristics were prevalent, such as:
  - Unmutated IGHV locus (82%)
  - Del(17p) or *TP53* mutation (60%)
  - Complex karyotype (47%)

	Total (N=49)
Age, median (range), years	70 (50-91)
Male sex, n (%)	31 (63)
ECOG PS, n (%)	
1	19 (39)
2	1 (2)
CLL/SLL risk characteristics at study entry, n/N (%)	
Binet stage C	23/46 (50)
Unmutated IGHV	32/39 (82)
del(17p) or *TP53* mutation	28/47 (60)
Complex karyotype (≥3 abnormalities)	15/32 (47)

	Total (N=49)
Mutation status, n/N (%)	
BTK mutation present	15/47 (32)
PLCG2 mutation present	6/47 (13)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	38 (78)
cBTK inhibitor	45 (92)
ncBTK inhibitor	11 (22)
BCL2 inhibitor	42 (86)
cBTK + BCL2 inhibitors	37 (76)
cBTK + ncBTK + BCL2 inhibitors	11 (22)
Discontinued BTK inhibitor due to PD, n/N (%)	40/45 (89)

cBTK, covalent BTK; ncBTK, noncovalent BTK.

Overall Safety Summary

- One DLT was reported (200-mg dose; grade 3 maculopapular rash)[a]
- None of the 3 TEAEs that led to death were considered related to treatment by the investigator

Patients, n (%)	Total (N=49)
Any TEAE	47 (96)
Any treatment-related	30 (61)
Grade ≥3	27 (55)
Treatment-related grade ≥3	13 (27)
Serious	21 (43)
Treatment-related serious	6 (12)
Leading to death[b]	3 (6)
Treatment-related leading to death	0
Leading to treatment discontinuation[c]	6 (12)
Treatment-related leading to treatment discontinuation	1 (2)
Leading to treatment modification	18 (37)
Dose interruption	18 (37)
Dose reduction	3 (6)

[a] DLTs were only assessed during the first 4 weeks of Part 1a. [b] (1) Septic shock (350 mg); (2) aspergillosis (350 mg); (3) pneumonia (200 mg) in the context of PD. [c] (1) Aspergillosis and cerebral aspergillosis (350 mg); (2) general physical health deterioration (350 mg) in the context of PD; (3) septic shock (350 mg); (4) pneumonia (200 mg) in the context of PD; (5) subdural hemorrhage (350 mg); (6) thyroid carcinoma (200 mg).

Most Frequent Adverse Events

Patients, n (%)	Total (N=49)[a]	
	All Grade	Grade ≥3
Fatigue	16 (33)	1 (2)
Contusion	14 (29)	0
Anemia	11 (22)	1 (2)
Diarrhea	11 (22)	0
Neutropenia/neutrophil count decreased	11 (22)	10 (20)
Pneumonia	8 (16)	6 (12)
COVID-19	7 (14)	0
Cough	7 (14)	0
Dyspnea	7 (14)	0
Amylase increased[b]	6 (12)	0
Lipase increased[b]	6 (12)	1 (2)
Pyrexia	6 (12)	0
Thrombocytopenia/platelet count decreased	6 (12)	0
Arthralgia	5 (10)	0
Decreased appetite	5 (10)	0
Nausea	5 (10)	0

No cases of atrial fibrillation or grade ≥3 hypertension were reported

[a] All grade TEAEs in ≥10% of patients. [b] All events were lab findings and were transient, mostly occurring during the first 1-3 cycles of treatment, with no clinical pancreatitis.

Overall Response Rate

- The ORR was 72% (31/43) in response-evaluable patients with CLL/SLL
- The ORR for the 200-mg group was 88%, with 2 patients achieving CR

	50 mg (n=1)	100 mg (n=5)	200 mg (n=16)	350 mg (n=14)	500 mg (n=7)	Total (N=43)
Best overall response, n (%)[a]						
CR	0	0	2 (13)	0	0	**2 (5)**
PR	1 (100)	4 (80)	10 (63)	6 (43)	1 (14)	**22 (51)**
PR-L	0	0	2 (13)	2 (14)	3 (43)	**7 (16)**
SD	0	1 (20)	1 (6)	2 (14)	3 (43)	**7 (16)**
PD	0	0	1 (6)	1 (7)	0	**2 (5)**
Discontinued prior to first assessment	0	0	0	3 (21)	0	**3 (7)**
ORR, n (%)[b]	**1 (100)**	**4 (80)**	**14 (88)[c]**	**8 (57)**	**4 (57)**	**31 (72)**
Disease control rate, n (%)[d]	1 (100)	5 (100)	15 (94)	10 (71)	7 (100)	**38 (88)**
Follow-up time, median, months	19.8	7.2	6.3	3.9	3.3	**4.6[e]**
Time to first response, median (range), months[f]	2.9 (2.9-2.9)	4.2 (2.8-6.2)	2.8 (2.6-4.1)	2.8 (2.6-5.6)	2.8 (2.6-2.8)	**2.8 (2.6-6.2)**

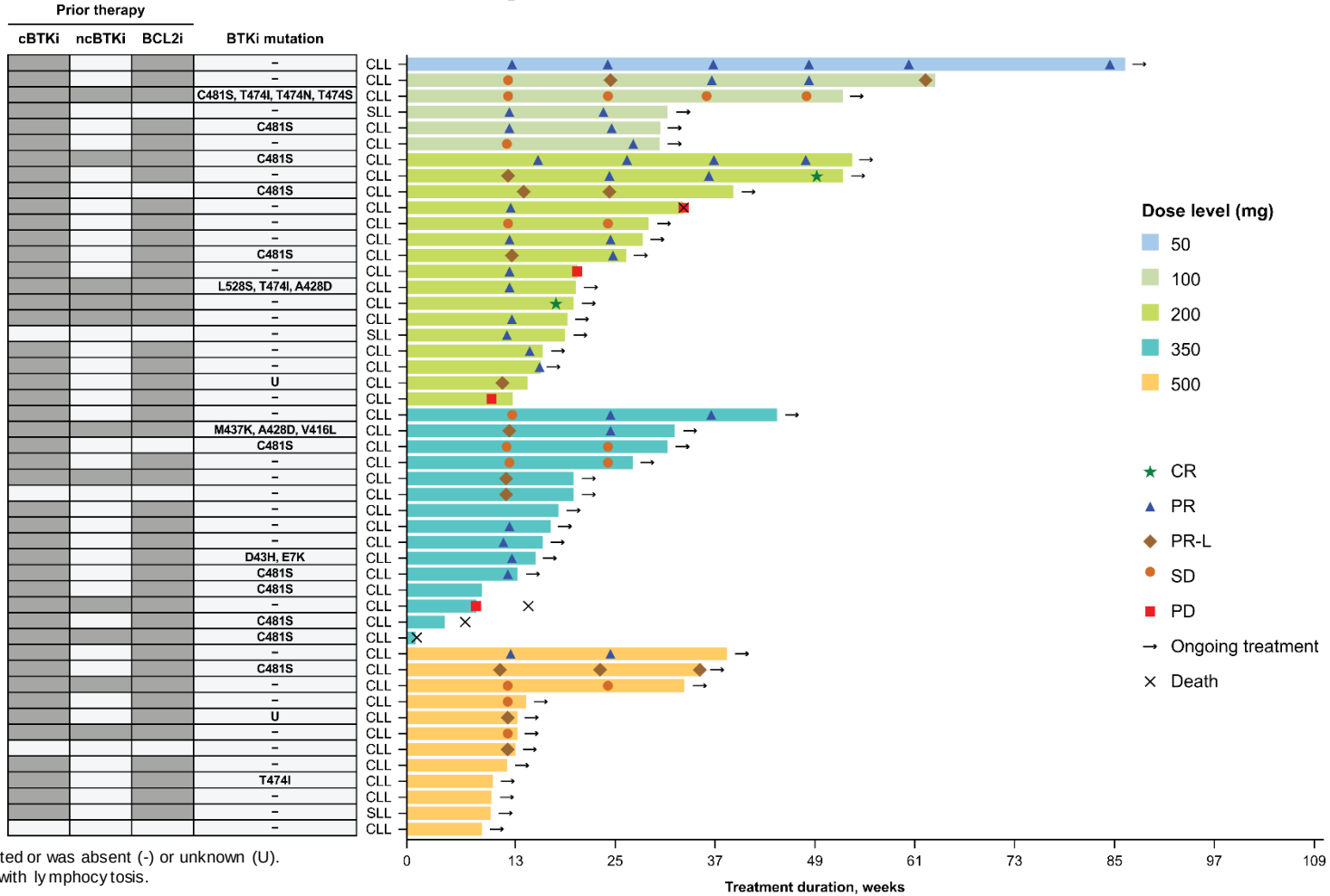
[a] Percentages may not sum to 100 due to rounding. [b] Proportion of patients who achieved a best overall response of PR-L or better. [c] One additional patient reported response after the February 14, 2024 data cut, indicating a 94% ORR (15/16 patients) in the 200-mg dose group. [d] Proportion of patients who achieved a best overall response of SD or better. [e] Study follow-up enrolled set N=49. [f] Time to first qualifying response in patients with a best overall response better than SD. PR-L, partial response with lymphocytosis.

Overall Response Rate

- The ORR was similar in patients who had:
  - Previously received cBTK + BCL2 inhibitors (70%)
  - Del(17p) or *TP53* mutation (68%)
  - Complex karyotype (67%)
- Responses have been observed in patients with C481S, T474I, and/or L528S *BTK* mutations, as well as patients with *PLCG2* mutations

cBTK, covalent BTK.

Treatment Duration and Response



BTK mutation status listed or was absent (-) or unknown (U).
PR-L, partial response with lymphocytosis.

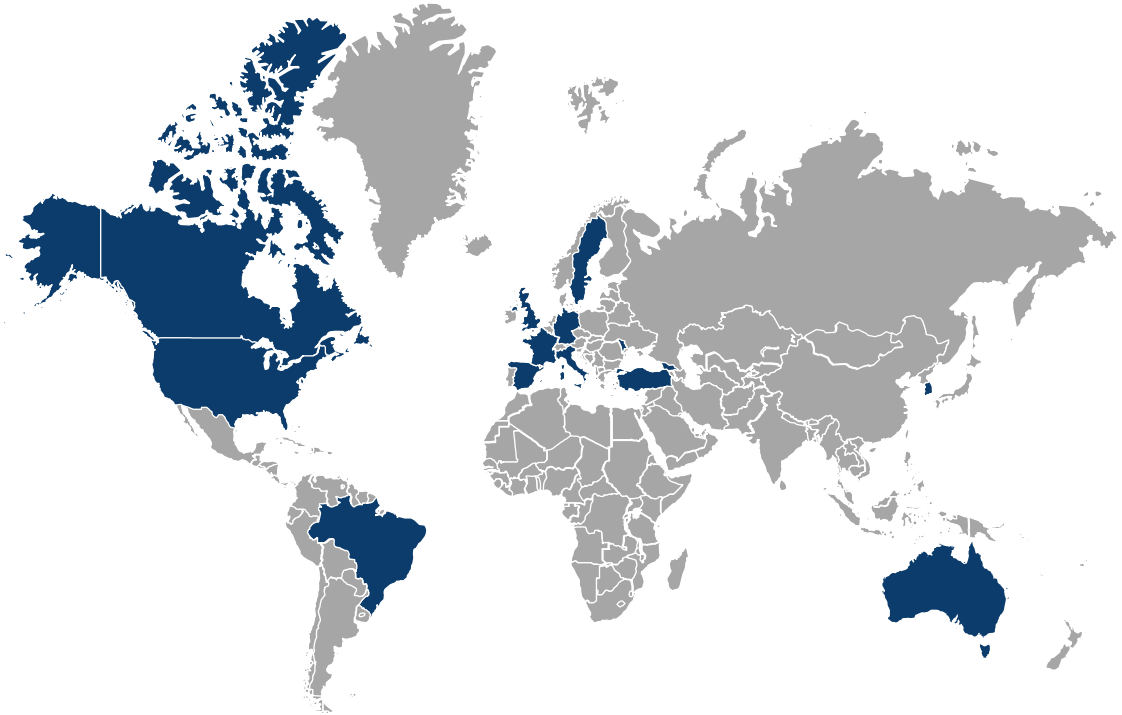
Conclusions

- In results from this ongoing first-in-human study, the novel BTK degrader BGB-16673 showed a generally well tolerated safety profile in this heavily pretreated CLL population
  - One DLT was reported and MTD was not reached
  - No atrial fibrillation or grade ≥3 hypertension has been reported so far
- There was promising antitumor activity, including in patients with BTK inhibitor–resistant mutations and those previously exposed to cBTK inhibitors, ncBTK inhibitors, and BCL2 inhibitors
  - ORR was 72% (31/43) with an 88% ORR in the 200-mg group, including 2 CRs[a]
  - Median time to first response was 2.8 months
  - Responses may continue to evolve as the study continues beyond the median 4.6-month follow-up
- A phase 2 cohort of patients with CLL/SLL exposed to both a cBTK inhibitor and BCL2 inhibitor is now enrolling
- These data support promising clinical activity of BGB-16673 in treatment of patients with CLL/SLL

[a] One additional patient reported response after the February 14, 2024 data cut, indicating a 94% ORR (15/16 patients) in the 200-mg dose group.
cBTK, covalent BTK; ncBTK, noncovalent BTK.

CaDAnCe-101 Study Sites (Recruiting)

- Enrollment for the CaDAnCe-101 study part 1c and phase 2 is ongoing at 90 of 115 planned study sites across the US, Canada, UK, France, Georgia, Germany, Italy, Moldova, Spain, Sweden, Turkey, Australia, South Korea, and Brazil



Acknowledgments

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Thank you