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

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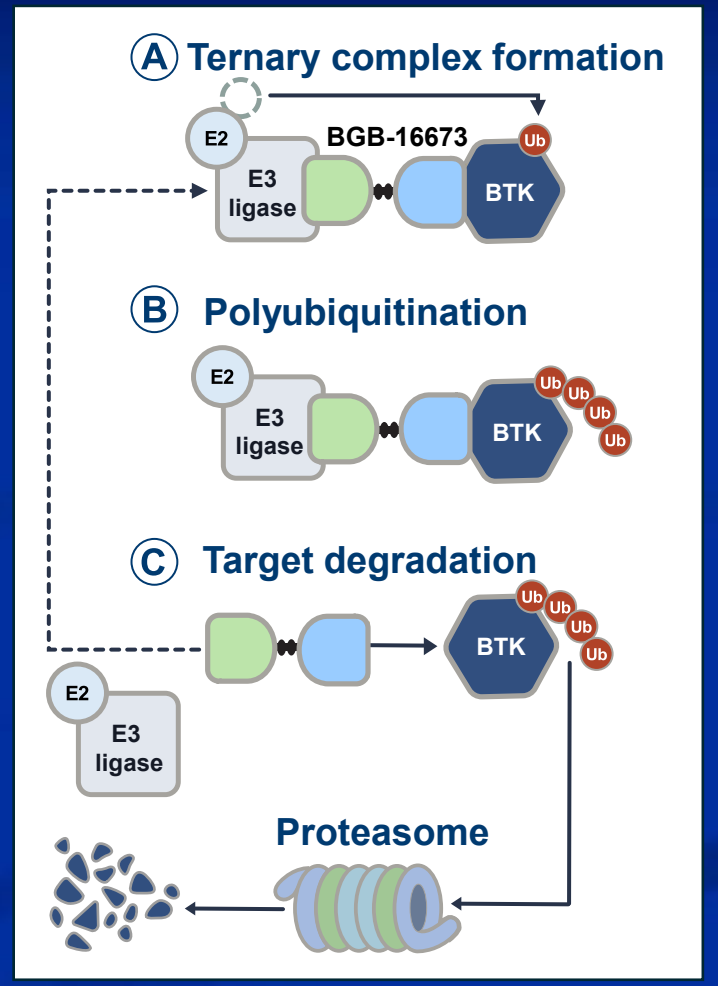
BGB-16673: A Chimeric Degradation Activating Compound (CDAC)

- 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 an orally available protein degrader that blocks BTK signaling by tagging BTK for degradation through the cell's proteasome pathway, leading to tumor regression[4]
- 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)[4,5]
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue[6]
- Here, updated safety and efficacy results in patients with R/R CLL/SLL in phase 1 of CaDAnCe-101 are presented



BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CNS, central nervous system; ncBTK, noncovalent Bruton tyrosine kinase; R/R, relapsed/refractory; 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: A 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] & tolerability, MTD, & RDFE
- **Secondary:** PK, PD, & 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–naïve 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 other criteria were met for treatment discontinuation. [c]Safety was assessed according to Common Terminology Criteria for Adverse Events v5.0 in all patients and iwCLL hematologic toxicity criteria in patients with CLL. [d]Response was assessed per iwCLL 2018 criteria after 12 weeks in patients with CLL.
cBTKi, covalent Bruton tyrosine kinase inhibitor; 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; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; R/R, relapsed/refractory; RDFE, recommended dose for expansion; RT, Richter transformation; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

Baseline Patient Characteristics

Heavily pretreated, with high-risk CLL features

	Total (N=66)
Age, median (range), years	70 (47-91)
Male, n (%)	45 (68.2)
ECOG PS, n (%)	
0	38 (57.6)
1	27 (40.9)
2	1 (1.5)
CLL/SLL risk characteristics at study entry, n/N with known status (%)	
Binet stage C	29/62 (46.8)
Unmutated IGHV	38/49 (77.6)
del(17p) and/or *TP53* mutation	43/66 (65.2)
Complex karyotype (≥3 abnormalities)	22/44 (50.0)

	Total (N=66)
Mutation status, n/N (%)	
BTK mutation present	24/63 (38.1)
PLCG2 mutation present	10/63 (15.9)
BTK and *PLCG2* mutation present	5/63 (7.9)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	47 (71.2)
cBTK inhibitor	62 (93.9)
ncBTK inhibitor	14 (21.2)
BCL2 inhibitor	54 (81.8)
cBTK + BCL2 inhibitors	42 (63.6)
cBTK + ncBTK + BCL2 inhibitors	12 (18.2)
Discontinued prior BTK inhibitor due to PD, n/N (%)[a]	55/62 (88.7)

Data cutoff: March 3, 2025.

[a]The remaining seven patients discontinued prior BTK inhibitor due to toxicity (n=4), treatment completion (n=2), and other (n=1).

BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; ncBTK, noncovalent Bruton tyrosine kinase; PD, progressive disease; SLL, small lymphocytic lymphoma.

Overall Safety Summary

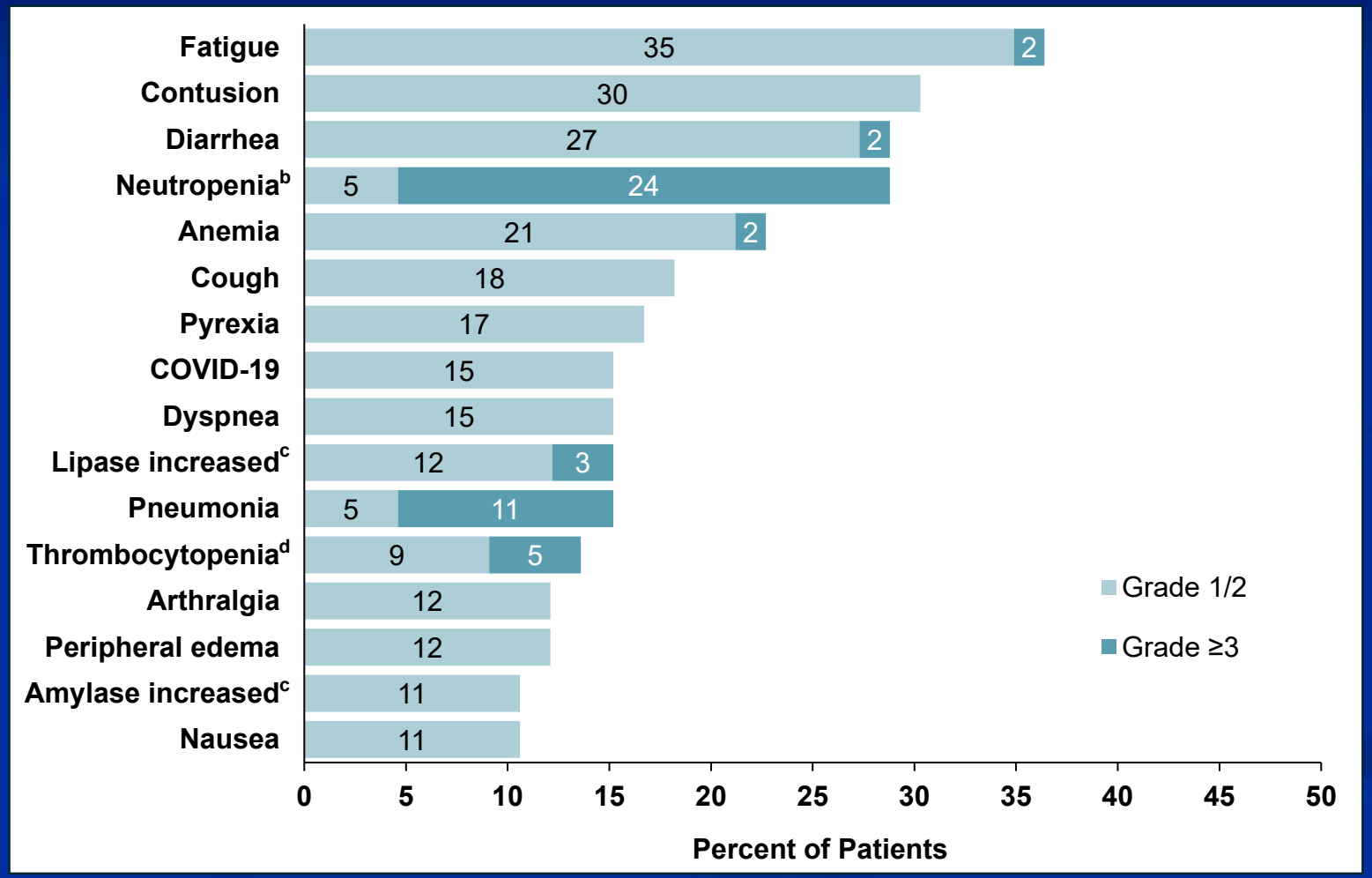
Tolerable safety profile, with no treatment-related TEAEs leading to death

Patients, n (%)	Total (N=66)
Any TEAE	63 (95.5)
Any treatment-related	49 (74.2)
Grade ≥3	40 (60.6)
Treatment-related grade ≥3	20 (30.3)
Serious	30 (45.5)
Treatment-related serious	8 (12.1)
Leading to death	4 (6.1)
Treatment-related leading to death	0
Leading to treatment discontinuation	9 (13.6)
Treatment-related leading to treatment discontinuation	2 (3.0)

Median follow-up in safety-evaluable patients: 15.6 months (range, 0.3-30.6+ months).
TEAE, treatment-emergent adverse event.

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

- Most common TEAEs were fatigue in 37% and contusion (bruising) in 30% of patients
- Atrial fibrillation: n=2 (one grade 1 and one grade 2 in the context of infection and PD, respectively)
- Major hemorrhage[a]: n=2 (one grade 1 subarachnoid hemorrhage and one grade 3 subdural hemorrhage)
  - No new events occurred since the last update
- No pancreatitis



Median follow-up in safety-evaluable patients: 15.6 months (range, 0.3-30.6+ months).
[a]Grade ≥3, serious, or any central nervous system bleeding [b]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [c]All events were laboratory findings and were transient, mostly occurring during the first 1-3 cycles of treatment, with no clinical pancreatitis. [d]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.
PD, progressive disease; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Overall Response Rate

Significant responses, particularly at 200-mg dose level

	50 mg (n=1)	100 mg (n=22)	200 mg (n=16)	350 mg (n=15)	500 mg (n=12)	Total (N=66)
Best overall response, n (%)						
CR/CRi	0	1 (4.5)	1 (6.3)	0	1 (8.3)	**3 (4.5)**
PR[a]	1 (100)	11 (50.0)	12 (75.0)	11 (73.3)	9 (75.0)	44 (66.7)
PR-L	0	6 (27.3)	2 (12.5)	0	1 (8.3)	9 (13.6)
SD	0	4 (18.2)	0	0	1 (8.3)	5 (7.6)
PD	0	0	1 (6.3)	1 (6.7)	0	2 (3.0)
Discontinued prior to first assessment	0	0	0	3 (20.0)	0	3 (4.5)
Overall response rate, n (%)[b]	1 (100)	18 (81.8)	**15 (93.8)**	11 (73.3)	11 (91.7)	**56 (84.8)**
Time to first response, median (range), months[c]	2.9 (2.9-2.9)	2.8 (2.0-6.2)	2.9 (2.6-8.3)	2.8 (2.6-19.4)	2.8 (2.6-13.8)	2.8 (2.0-19.4)
Time to best response, median (range), months	2.9 (2.9-2.9)	2.8 (2.0-11.1)	3.4 (2.6-13.8)	5.6 (2.6-19.4)	8.3 (2.7-13.8)	3.4 (2.0-19.4)
Duration of exposure, median (range), months	29.6 (29.6-9.6)	7.1 (3.7-23.7)	16.2 (2.9-24.6)	15.6 (0.2-22.8)	15.3 (6.8-21.4)	12.9 (0.2-29.6)

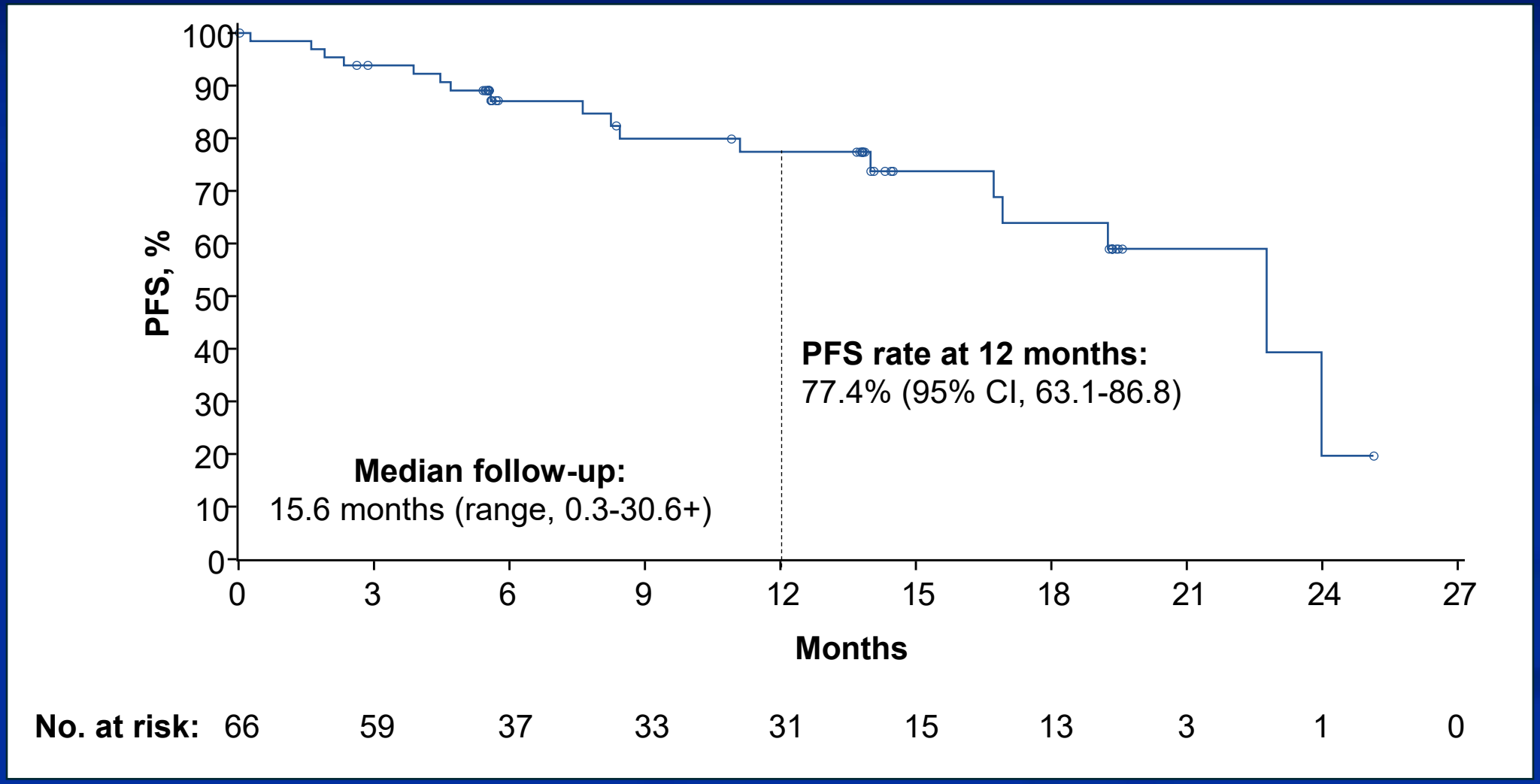
[a]Of 44 patients with PR, 12 achieved all nodes normalized. [b]Includes best overall response of PR-L or better. [c]In patients with a best overall response of PR-L or better.
CR, complete response; CRi, complete response with incomplete marrow recovery; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

High Overall Response Rates in High-Risk Subgroups

Subgroup	ORR, n/N with known status (%)
Double exposure (previously received cBTKi + BCL2i)	38/42 (90.5)
Triple exposure (previously received cBTKi + ncBTKi + BCL2i)	9/12 (75.0)
del(17p) and/or *TP53* mutation	35/43 (81.4)
Complex karyotype (≥3 abnormalities)	16/22 (72.7)
***BTK* mutations**	18/24 (75.0)
***PLCG2* mutations**	9/10 (90.0)

BCL2i, BCL2 inhibitor; cBTKi, covalent Bruton tyrosine kinase inhibitor; ncBTKi, noncovalent Bruton tyrosine kinase inhibitor; ORR, overall response rate.

Progression-Free Survival



PFS, progression-free survival.

Conclusions

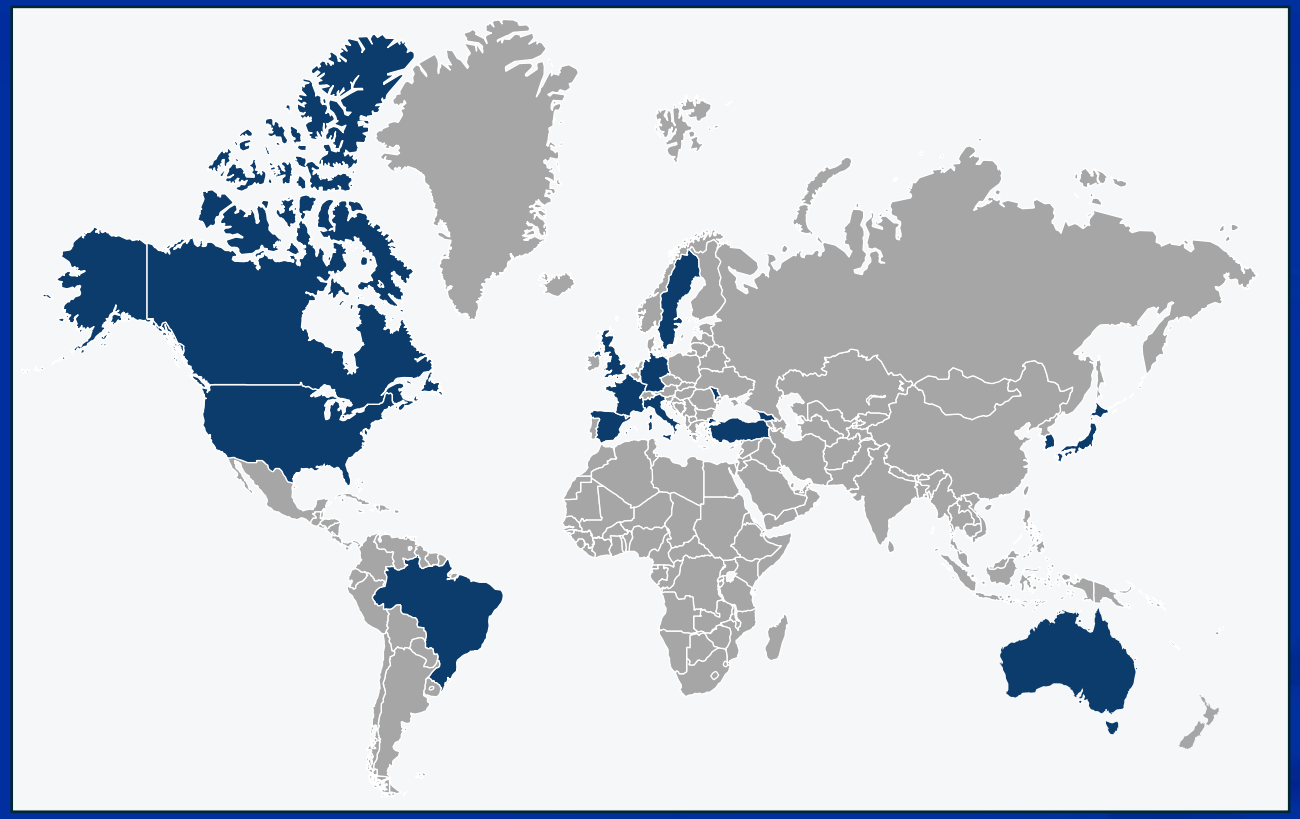
- In phase 1 of CaDAnCe-101, the novel BTK degrader **BGB-16673** was **safe** and **well tolerated** in this **heavily pretreated** population of patients with R/R **CLL/SLL**
  - Only 2 patients discontinued treatment due to a treatment-related TEAE
  - No treatment-related deaths occurred
  - The 200-mg dose was selected as the RDFE for phase 2

- Significant **antitumor activity** was observed, including in patients with ***BTK* mutations** and those **previously exposed to cBTK, ncBTK, and BCL2 inhibitors**
  - ORR was 84.8%, and CR/CRi rate was 4.5%; in the 200-mg dose group, ORR was 93.8%
  - ORR in triple-exposed patients: 75.0%
  - Median time to first response: 2.8 months
  - PFS rate at 12 months: 77.4%
  - 65.2% of patients still on treatment with a median follow-up of 15.6 months

- **BGB-16673** is being evaluated in **ongoing phase 2 and phase 3** studies in **R/R CLL**

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, Brazil, and Japan



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