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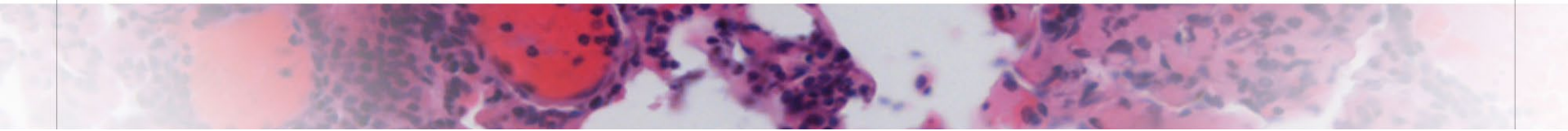

Updated Efficacy and Safety Results of the Bruton Tyrosine Kinase Degrader BGB-16673 in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma From the Ongoing Phase 1 CaDAnCe-101 Study

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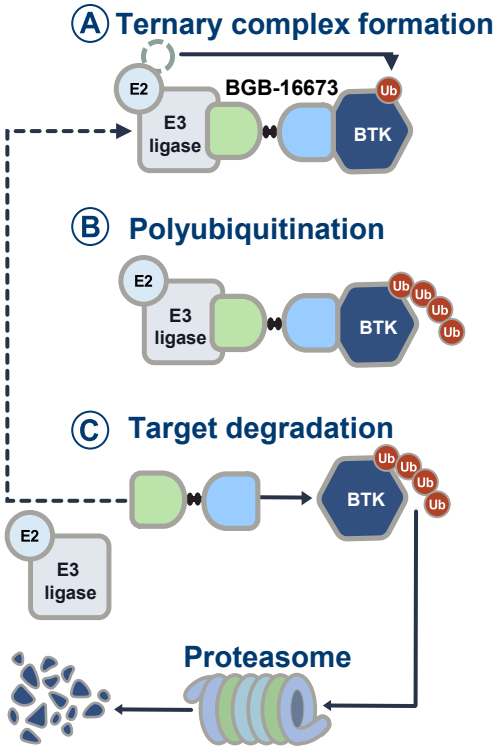
CaDAnCe-101

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

- 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 highly selective, orally available BTK protein degrader that:
  - Blocks BCR signaling by mediating BTK degradation through the proteasome pathway[4]
  - Disrupts both the catalytic activity of BTK and its protein scaffolding functions[5,6]
  - Does not require sustained target binding; a single BGB-16673 molecule can degrade multiple BTK proteins[6]
  - Has broad mutation coverage for *BTK* mutations associated with covalent and noncovalent BTK inhibitor resistance[4,7]
    - Led to maximal degradation of BTK in clinical samples regardless of *BTK* mutation status[8]
  - Showed CNS penetration in preclinical models[7]
- Here, updated safety and efficacy results in patients with R/R CLL/SLL in phase 1 of CaDAnCe-101 are presented



BCR, B cell receptor; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CNS, central nervous system; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; 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. Békés M, et al. *Nat Rev Drug Discov*. 2022;21(3):181-200; 6. Chirnomas D, et al. *Nat Rev Clin Oncol*. 2023;20(4):265-278; 7. Wang H, et al. EHA 2023. Abstract P1219; 8. 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

- Meets iwCLL 2018 criteria for treatment
- ≥2 prior therapies, including cBTKi if approved for their disease
- ECOG PS 0-2 (0-1 in the EU)
- Adequate organ function

Key objectives for part 1

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

Part 1: Monotherapy dose finding[a]

Part 1a: Dose escalation[b]
Selected R/R B-cell malignancies
(MZL, FL, MCL, **CLL/SLL**, WM, DLBCL, RT)
n≤72
Oral, QD, 28-day cycle
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 other criteria were met for treatment discontinuation. [c]Safety was assessed according to NCI-CTCAE v5.0 in all patients and iwCLL hematologic toxicity criteria in patients with CLL. [d]Response was assessed per iwCLL 2018 criteria with partial response with lymphocytosis modification for CLL and per 2014 Lugano criteria for SLL, with the first response assessment after 12 weeks of treatment.

BTK, Bruton tyrosine kinase; 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; QD, once daily; 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=68)
Age, median (range), years	70 (47-91)
Male, n (%)	47 (69.1)
ECOG PS, n (%)	
0	38 (55.9)
1	29 (42.6)
2	1 (1.5)
CLL/SLL risk characteristics at study entry, n/N with known status (%)	
Binet stage C	29/64 (45.3)
Unmutated IGHV	38/49 (77.6)
del(17p) and/or *TP53* mutation	46/68 (67.6)
Complex karyotype (≥3 abnormalities)	22/44 (50.0)

	Total (N=68)
Mutation status, n/N (%)	
BTK mutation present	26/66 (39.4)
PLCG2 mutation present	10/66 (15.2)
BTK and *PLCG2* mutation present	5/66 (7.6)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	49 (72.1)
cBTK inhibitor	64 (94.1)
ncBTK inhibitor	14 (20.6)
BCL2 inhibitor	56 (82.4)
cBTK + BCL2 inhibitors	44 (64.7)
cBTK + ncBTK + BCL2 inhibitors	12 (17.6)
Discontinued prior BTK inhibitor due to PD, n/N (%)[a]	57/64 (89.1)

Data cutoff: August 22, 2025.

[a]The remaining seven patients discontinued prior BTK inhibitor due to toxicity (n=4) and other (n=3).

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; IGHV, immunoglobulin heavy chain variable region; ncBTK, noncovalent Bruton tyrosine kinase; PD, progressive disease; SLL, small lymphocytic lymphoma.

Overall Safety Summary

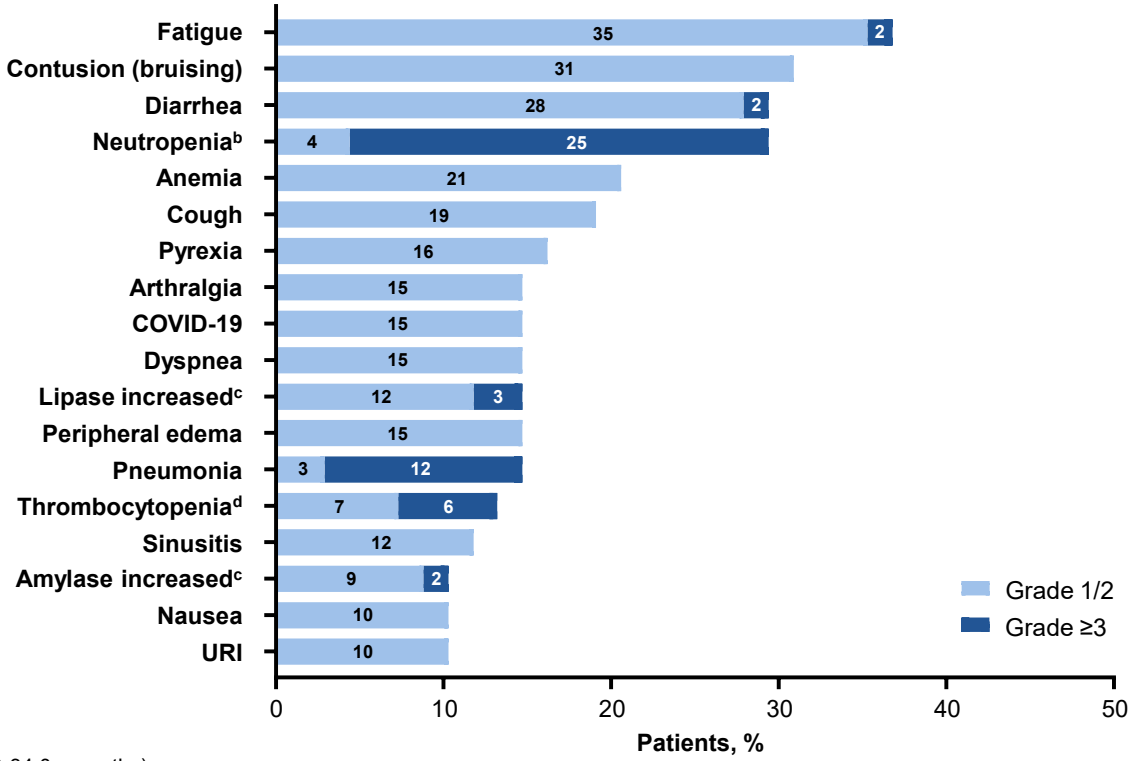
Tolerable safety profile, with no treatment-related TEAEs leading to death

Patients, n (%)	Total (N=68)
Any TEAE	65 (95.6)
Any treatment-related	52 (76.5)
Grade ≥3	42 (61.8)
Treatment-related grade ≥3	23 (33.8)
Serious	33 (48.5)
Treatment-related serious	9 (13.2)
Leading to death	5 (7.4)
Treatment-related leading to death	0
Leading to treatment discontinuation	12 (17.6)
Treatment-related leading to treatment discontinuation	3 (4.4)

Median study follow-up in safety-evaluable patients: 19.8 months (range, 0.3-34.0+ months).
TEAE, treatment-emergent adverse event.

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

- The most common TEAEs were fatigue (36.8%) and contusion (bruising; 30.9%)
- Grade ≥3 neutropenia: n=17 (25.0%); 16 patients (23.5%) had grade ≥2 neutropenia at baseline
  - Neutropenic fever: n=1
- Atrial fibrillation: n=3 (grade 1, n=1; grade 2, n=2; all transient (2 of them lasting 1 day) in the context of infection and PD, assessed as unrelated to treatment)
- Treatment-related major hemorrhage[a]: n=2 (one grade 3 subdural hemorrhage and one grade 3 post-procedural hematuria)



Median follow-up in safety-evaluable patients: 19.8 months (range, 0.3-34.0+ months).

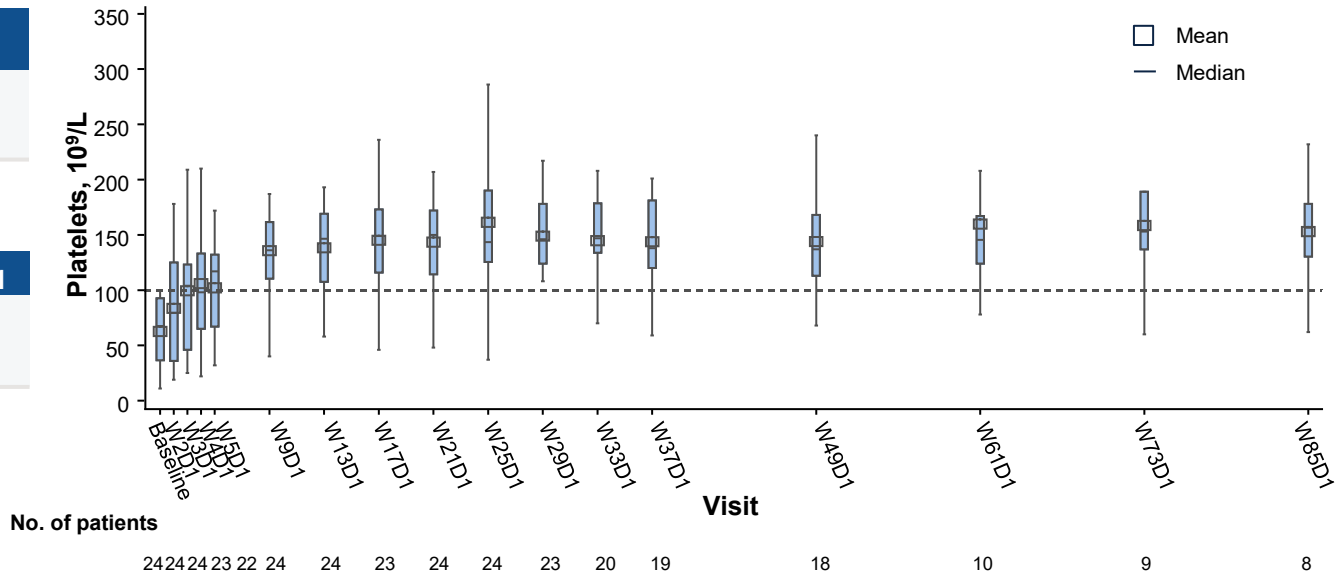
[a]Grade ≥3, serious, or any central nervous system bleeding. [b]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [c]All events were laboratory findings and were transient, mostly occurring during the first 1-3 cycles of treatment, with no clinical pancreatitis. [d]Thrombocytopenia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

PD, progressive disease; TEAE, treatment-emergent adverse event; URI, upper respiratory tract infection.

Rapid and Significant Cytopenia Improvement Was Observed in Patients With Treatment Response

	Baseline	W9D1
Platelet count,[a] median, 10^9/L	67.5	136.0
Neutrophil count,[b] median, 10^9/L	1.1	2.4
	Baseline	**W13D1**
Hemoglobin level,[c] median, g/L	99.0	111.0

Platelet Count in Patients Who Had Baseline Thrombocytopenia and Responded to Treatment



[a]In n=24 patients based on 100×10^9/L cutoff. [b]In n=14 patients based on 1.5×10^9/L cutoff. [c]In n=25 patients based on 11.0 g/dL cutoff.
D, day; W, week.

Overall Response Rate

Significant responses, particularly at 200-mg dose level

	50 mg (n=1)	100 mg (n=22)	200 mg (n=18)	350 mg (n=15)	500 mg (n=12)	Total (N=68)
Best overall response, n (%)						
CR/CRi	0	1 (4.5)	1 (5.6)	0	0	**2 (2.9)**
PR[a]	1 (100)	14 (63.6)	12 (66.7)	11 (73.3)	11 (91.7)	49 (72.1)
PR-L	0	2 (9.1)	4 (22.2)	0	1 (8.3)	7 (10.3)
SD	0	5 (22.7)	0	0	0	5 (7.4)
PD	0	0	1 (5.6)	1 (6.7)	0	2 (2.9)
Discontinued prior to first assessment	0	0	0	3 (20.0)	0	3 (4.4)
ORR, n (%)[b]	1 (100)	17 (77.3)	**17 (94.4)**	11 (73.3)	12 (100)	**58 (85.3)**
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)	2.9 (2.6-19.4)	2.8 (2.7-13.8)	2.8 (2.0-19.4)
Time to best response, median (range), months	2.9 (2.9-2.9)	2.9 (2.0-11.1)	3.0 (2.6-13.8)	5.6 (2.6-19.4)	8.4 (2.7-13.8)	4.2 (2.0-19.4)
Duration of exposure, median (range), months	29.6 (29.6-29.6)	12.3 (3.4-25.4)	14.4 (2.9-30.3)	19.8 (0.2-28.5)	20.4 (6.8-27.1)	13.6 (0.2-30.3)

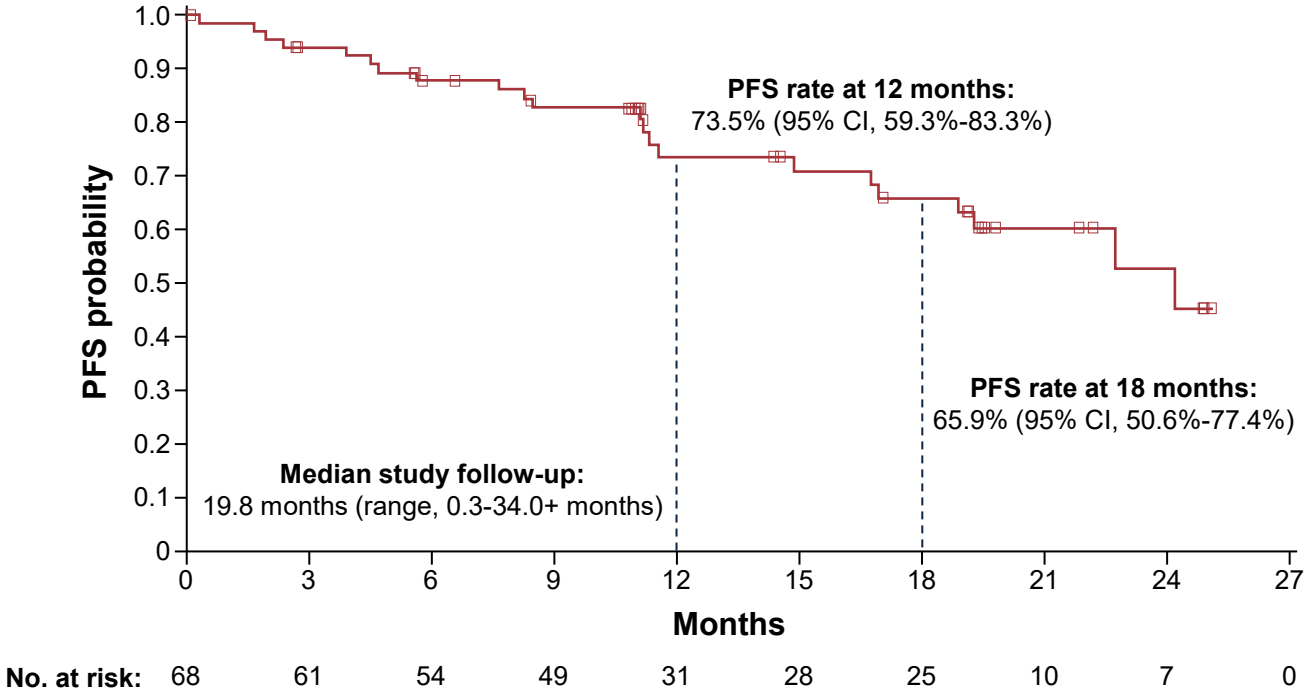
[a]Of 49 patients with PRs,16 achieved all nodes normalized. [b]Includes best overall response of PR-L or better. [c]In patients with a best overall response of PR-L or better.
CR, complete response; CRi, complete response with incomplete marrow recovery; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

High Overall Response Rates in High-Risk Subgroups

Characteristic, n/N with known status (%)	ORR
Prior cBTKi + BCL2i	41/44 (93.2)
Prior cBTKi + BCL2i + ncBTKi	9/12 (75.0)
6 or more prior lines of therapy	13/16 (81.3)
del(17p) and/or *TP53* mutation	37/46 (80.4)
Complex karyotype (≥3 abnormalities)	16/22 (72.7)
***BTK* mutations**	20/26 (76.9)
***PLCG2* mutations**	9/10 (90.0)

BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent Bruton tyrosine kinase inhibitor; ncBTKi, noncovalent Bruton tyrosine kinase inhibitor; ORR, overall response rate.

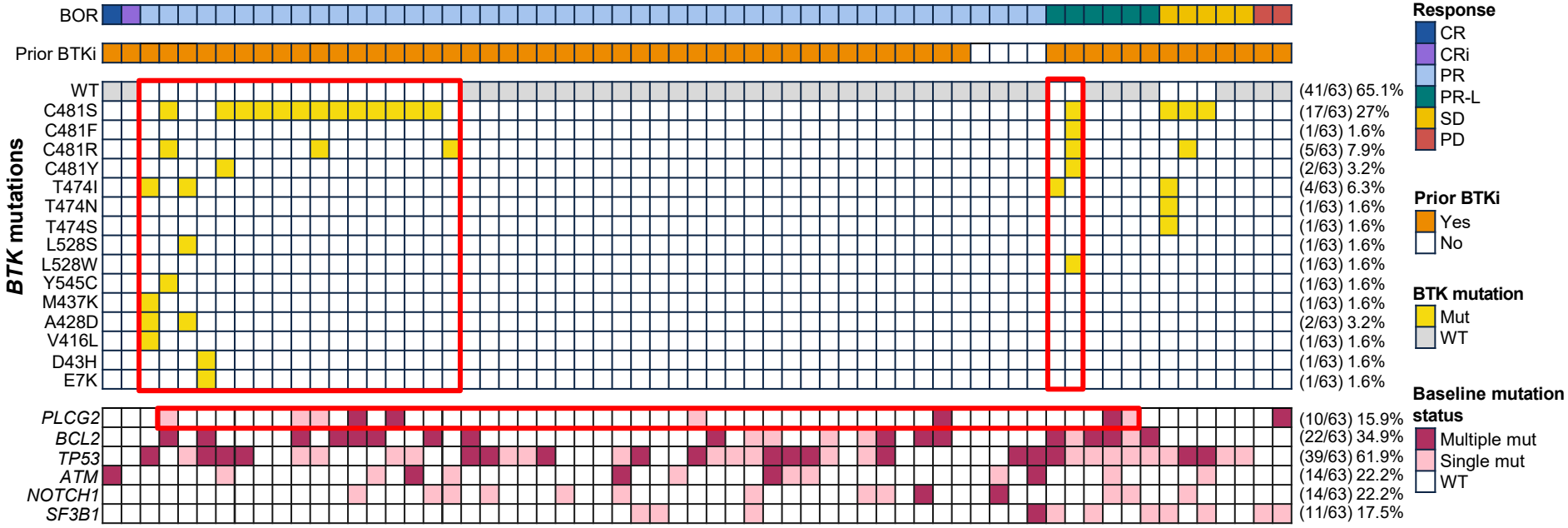
Progression-Free Survival



PFS, progression-free survival.

Responses Occurred Regardless of Specific Mutations

Best overall response vs baseline mutation[a]

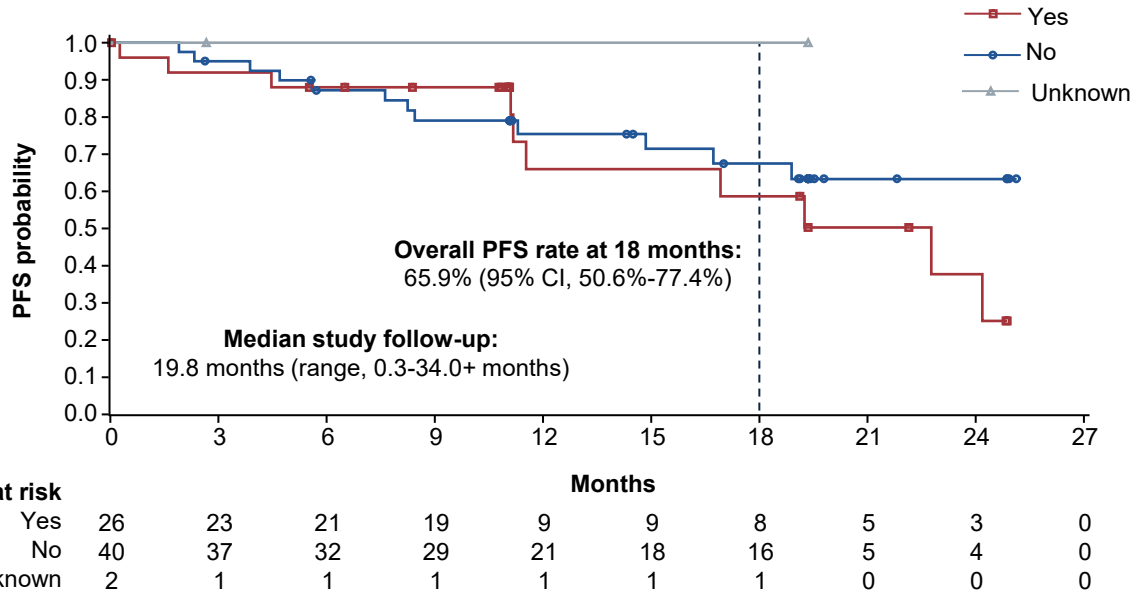


[a]Genomic mutations were centrally assessed by targeted next-generation sequencing.

BOR, best overall response; BTKi, Bruton tyrosine kinase inhibitor; CR, complete response; CRi, complete response with incomplete marrow recovery; mut, mutation; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; WT, wild type.

Progression-Free Survival was Consistent Across Baseline *BTK* Mutation Status

BTK mutation status	18-month PFS rate, % (95% CI)
Yes	58.7 (30.6-78.7)
No	67.5 (48.2-80.9)
Unknown	100 (100-100)



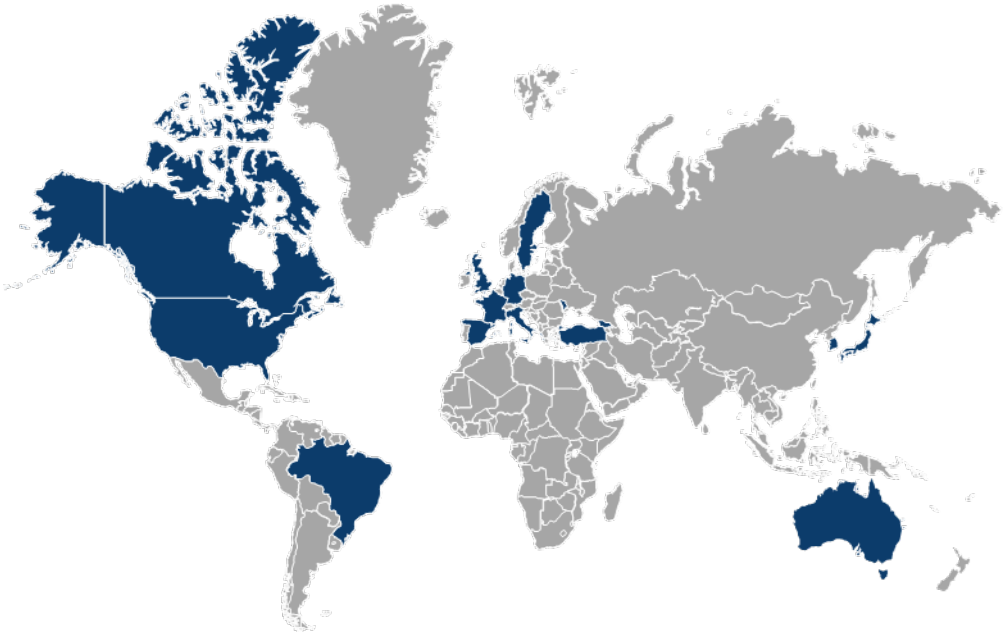
PFS, progression-free survival.

Conclusions

- In the phase 1 CaDAnCe-101 study, the novel BTK degrader **BGB-16673** was **well tolerated** in this heavily pretreated population of patients with R/R **CLL/SLL**
  - Three patients discontinued treatment due to a treatment-related TEAE
  - No treatment-related deaths
  - No new toxicities identified with a median treatment duration of 13.6 months
- Significant **antitumor activity** was observed, regardless of ***BTK* mutation status,** prior **cBTK, ncBTK, and BCL2 inhibitors;** and number of prior lines of therapy
  - ORR was 85.3% and CR/CRi rate was 2.9%; in the 200-mg dose group, ORR was 94.4%
  - ORR was 75.0% in patients with prior cBTKi, BCL2i, and ncBTKi
  - Sustained disease control as evidenced by a PFS rate of 65.9% at 18 months with a median study follow-up of 19.8 months, with 54.4% of patients remaining on treatment
- Promising responses seen in RT (Thompson et al, abstract 3895, poster on Dec 7)
- **BGB-16673** is being evaluated in **ongoing phase 2 and phase 3** studies in **R/R CLL**

Study Status

- 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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