Tacabrutideg (BGB-16673), A Bruton Tyrosine Kinase Degrader, in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: A Phase 1 CaDAnCe-101 Study Update

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CaDAnCe-101

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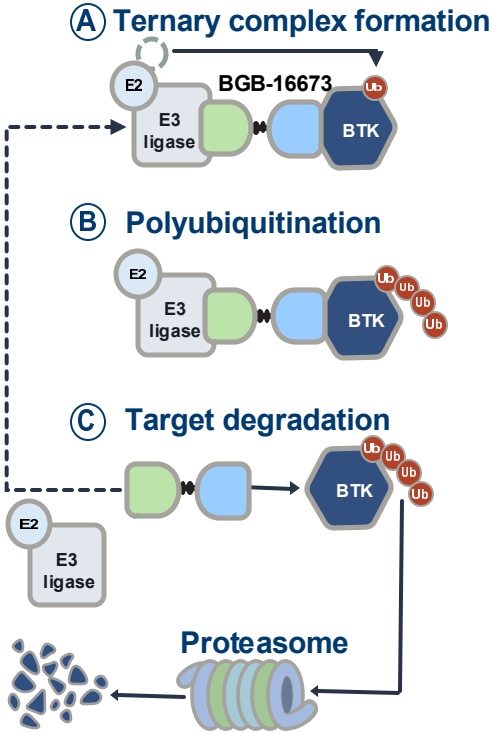
Tacabrutideg (BGB-16673): A Potential First-in-Class BTK Degrader

- Patients with CLL/SLL experience disease progression with BTK inhibitors, which can be caused by resistance mutations in *BTK*[1-3]
- Tacabrutideg is a potential first-in-class oral BTK degrader that induces BTK degradation through the proteasome pathway, leading to tumor regression[4]
  - Degrades wild-type BTK and many BTK mutations associated with resistance to covalent and noncovalent BTK inhibitors with the broadest activity among BTK-targeting agents[4,5]
  - Disrupts BTK kinase activity and its ability to transduce signals through its scaffolding function, in contrast to BTK inhibitors that only block kinase activity[6,7]
  - A single tacabrutideg molecule can degrade multiple BTK proteins[7]
  - Demonstrates CNS penetration in preclinical models[8]
  - Drives robust clinical responses across several B-cell malignancies[9]
- Here, we report updated safety and efficacy results for phase 1 of the CaDAnCe-101 trial in patients with R/R CLL/SLL



BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CNS, central nervous system; R/R, relapsed/refractory; Ub, ubiquitin.

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CaDAnCe-101: CLL/SLL-Inclusive Cohorts

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≤75

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 National Cancer Institute 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 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/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; 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; WM, Waldenström macroglobulinemia.

Baseline Patient Characteristics

Heavily pretreated, with high-risk CLL features

	Total (N=67)
Age, median (range), years	70 (47-91)
Male, n (%)	46 (68.7)
ECOG PS, n (%)	
0	38 (56.7)
1	28 (41.8)
2	1 (1.5)
CLL/SLL risk characteristics, n/N (%)	
Unmutated IGHV	43/56 (76.8)
del(17p) and/or *TP53* mutation	44/67 (65.7)
Complex karyotype (≥3 abnormalities)	23/43 (53.5)
Mutation status, n/N (%)	
BTK mutation present	25/66 (37.9)
PLCG2 mutation present	10/66 (15.2)
BTK and *PLCG2* mutation present	5/66 (7.6)

	Total (N=67)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	48 (71.6)
cBTK inhibitor	63 (94.0)
ncBTK inhibitor	14 (20.9)
BCL2 inhibitor	55 (82.1)
cBTK + BCL2 inhibitors (no ncBTK inhibitor)	43 (64.2)
cBTK + ncBTK + BCL2 inhibitors	12 (17.9)
Refractory to last cBTK inhibitor + last BCL2 inhibitor[a]	37/41 (90.2)
Discontinued prior BTK inhibitor due to PD, n/N (%)[b]	56/63 (88.9)

Data cutoff: February 25, 2026. Median study follow-up: 25.4 (range, 0.3-40.1) months.

[a]Refractory status in 14/55 patients with prior cBTK inhibitor and BCL2 inhibitor is unknown. [b]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/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain variable region; ncBTK, noncovalent Bruton tyrosine kinase; PD, progressive disease; PLCG2, phospholipase C gamma 2.

Overall Safety Summary

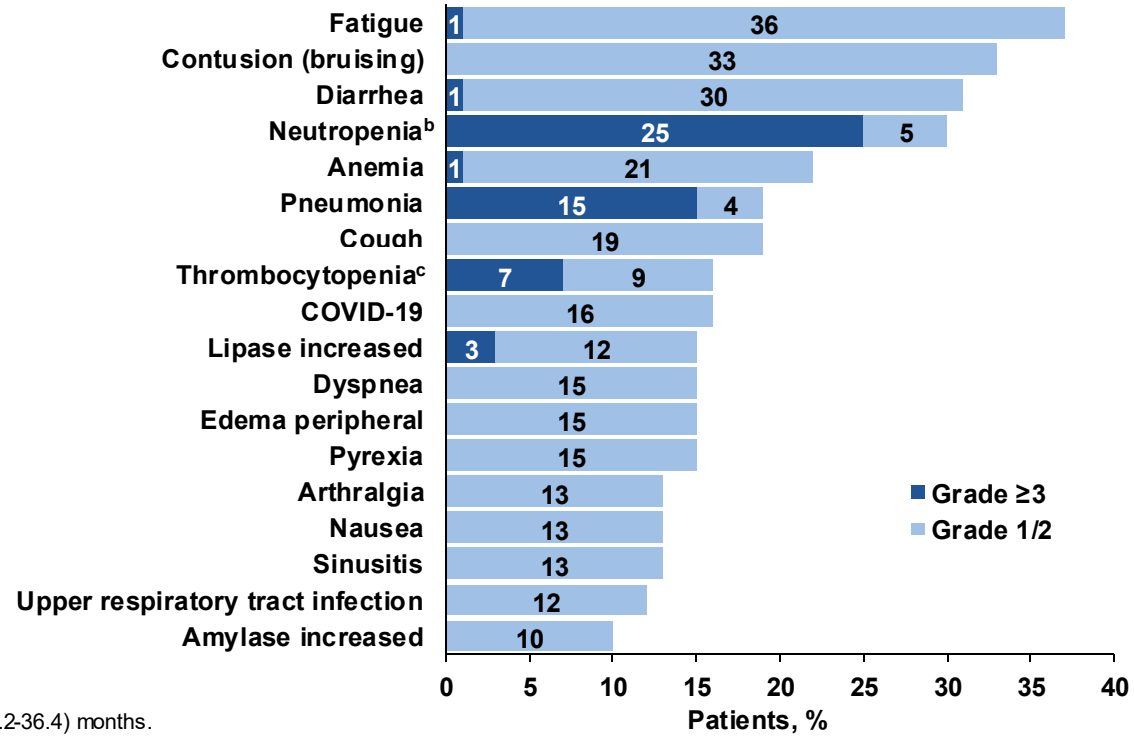
Tolerable safety profile

Patients, n (%)	Total (N=67)
Any TEAE	65 (97.0)
Any treatment-related	52 (77.6)
Grade ≥3	42 (62.7)
Treatment-related	23 (34.3)
Serious	36 (53.7)
Treatment-related	9 (13.4)
Leading to dose reduction	9 (13.4)
Treatment-related	5 (7.5)
Leading to treatment discontinuation	12 (17.9)
Treatment-related	4 (6.0)
Leading to death	5 (7.5)
Treatment-related	0

Median duration of exposure: 18.2 (range, 0.2-36.4) months.
TEAE, treatment-emergent adverse event.

All-Grade TEAEs in ≥10% of All Patients

- Grade ≥3 neutropenia: n=17 (25.4%); 15 patients (22.4%) had grade ≥2 neutropenia at baseline
  - Febrile neutropenia: n=1
- Grade ≥3 infection: n=24 (35.8%)
- Atrial fibrillation: n=3 (grade 1 and 2); all transient (2 of them lasting 1 day and all in the context of infection and PD)
- Treatment-related major hemorrhage[a]: n=2 (one grade 3 subdural hematoma and one grade 3 post-procedural hematuria)
- No new cases of atrial fibrillation, major hemorrhage, and invasive fungal infections since the last data cutoff (August 22, 2025)

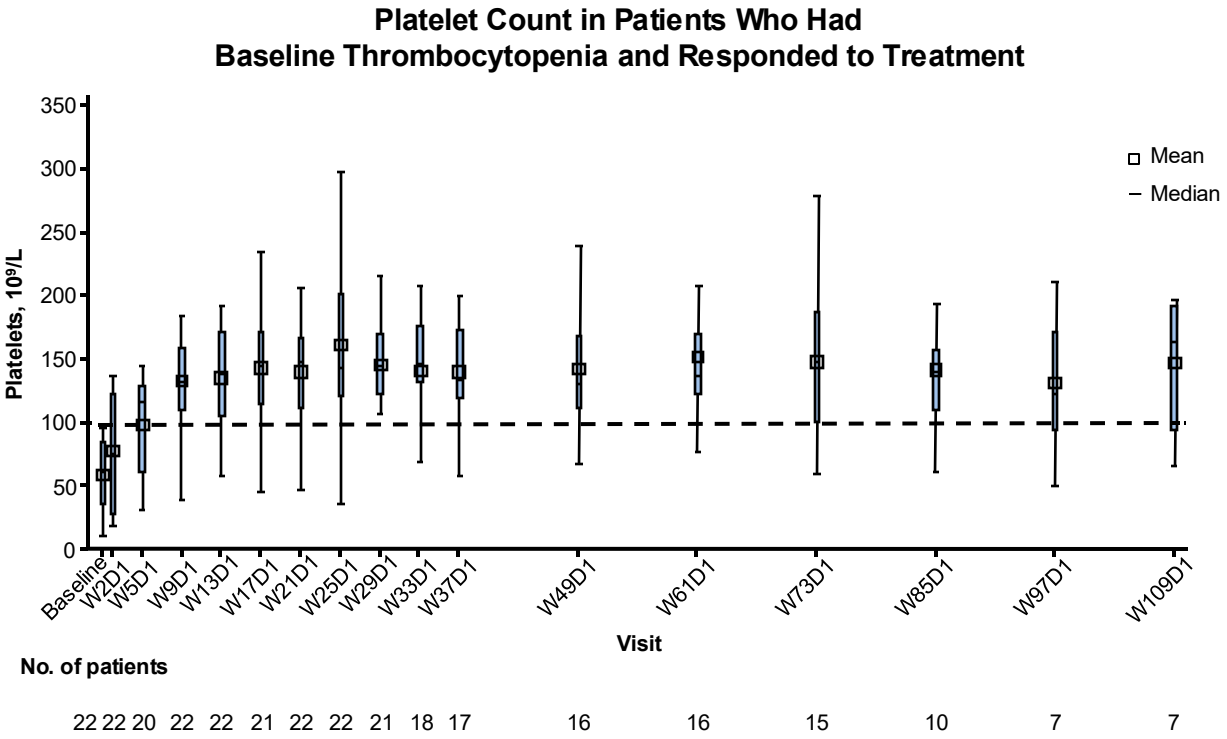


Data cutoff: February 25, 2026. Median duration of exposure: 18.2 (range, 0.2-36.4) months.
The values of any-grade TEAEs have been calculated from individual grade 1/2 and grade ≥3 values rounded to the nearest whole number.
[a]Grade ≥3, serious, or any central nervous system bleeding. [b]Neutropenia combines preferred terms *neutropenia* and *neutrophil count decreased*. [c]Thrombocytopenia combines preferred terms *thrombocytopenia* and *platelet count decreased*.
PD, progressive disease; TEAE, treatment-emergent adverse event.

Rapid and Sustained Cytopenia Improvement in Patients With Treatment Response

	Baseline	W9D1
Platelet count,[a] median (range), 10^9/L	62.5 (11.0-96.0)	133.5 (40.0-276.0)
Neutrophil count,[b] median (range), 10^9/L	1.1 (0-1.4)	2.6 (0-6.6)

	Baseline	W13D1
Hemoglobin level,[c] median (range), g/L	98.5 (71.0-109.0)	110.5 (87.0-128.0)



[a]In n=22 patients. [b]In n=13 patients. [c]In n=24 patients.
W, week; D, day.

Overall Response Rate

High and durable responses, particularly at the RP2D of 200 mg

	50 mg (n=1)	100 mg (n=22)	200 mg (n=17)	350 mg (n=15)	500 mg (n=12)	Total (N=67)
ORR, n (%)[a]	1 (100)	17 (77.3)	**16 (94.1)**	11 (73.3)	12 (100)	**57 (85.1)**
Best overall response, n (%)						
CR/CRi	0	1 (4.5)	1 (5.9)	0	0	**2 (3.0)**
PR[b]	1 (100)	14 (63.6)	14 (82.4)	11 (73.3)	11 (91.7)	51 (76.1)
PR-L	0	2 (9.1)	1 (5.9)	0	1 (8.3)	4 (6.0)
SD	0	5 (22.7)	0	0	0	5 (7.5)
PD	0	0	1 (5.9)	1 (6.7)	0	2 (3.0)
Discontinued prior to first assessment	0	0	0	3 (20.0)	0	3 (4.5)
Median time to first response (range), months[c]	2.9 (2.9-2.9)	2.8 (2.0-6.2)	2.8 (2.7-8.3)	2.9 (2.6-19.4)	2.8 (2.7-13.8)	2.8 (2.0-19.4)
Median time to best response, (range), months	2.9 (2.9-2.9)	2.9 (2.0-11.1)	3.5 (2.7-25.8)	5.6 (2.6-19.4)	8.4 (2.7-13.8)	5.5 (2.0-25.8)
Median duration of response, (range), months	NE (24.9-24.9)	16.6 (1.1-16.6)	20.6 (0.0-33.1)	NE (2.8-23.5)	16.2 (2.7-27.6)	20.7 (0.0-33.1)

[a]Proportion of patients who achieved a best overall response of PR-L or better. [b]19 / 51 PR pts had node normalization. [c]First response was assessed at 12 weeks.
CR, complete response; CRi, complete response with incomplete marrow recovery; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; RP2D, recommended phase 2 dose; SD, stable disease.

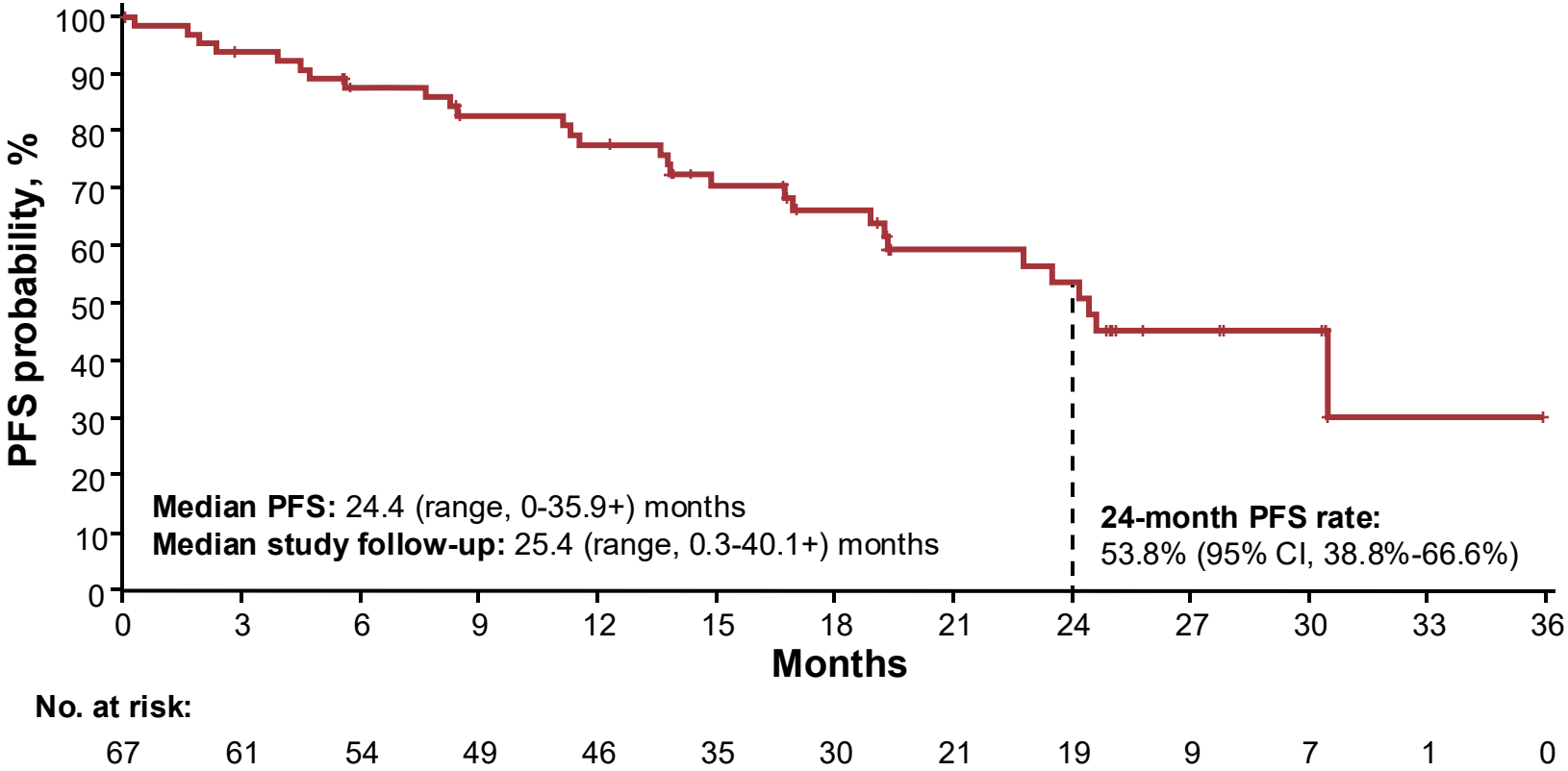
High Overall Response Rates in High-Risk Subgroups

Characteristic, n/N with known status (%)	ORR[a]
Prior cBTKi + BCL2i (no ncBTKi)	40/43 (93.0)
Prior cBTKi + ncBTKi + BCL2i	9/12 (75.0)
Refractory to last cBTKi + last BCL2i	31/37 (83.8)
5 or more prior lines of therapy	25/29 (86.2)
del(17p) and/or *TP53* mutation	35/44 (79.5)
Unmutated IGHV	38/43 (88.4)
Complex karyotype (≥3 abnormalities)	17/23 (73.9)
***BTK* mutation**	19/25 (76.0)
***PLCG2* mutation**	9/10 (90.0)

[a]PR-L or better.
BCL2i, B-cell lymphoma 2 inhibitor; BTK, Bruton tyrosine kinase; cBTKi, covalent Bruton tyrosine kinase inhibitor; IGHV, immunoglobulin heavy-chain variable region; ncBTKi, noncovalent Bruton tyrosine kinase inhibitor; ORR, overall response rate; PR-L, partial response with lymphocytosis.

Progression-Free Survival

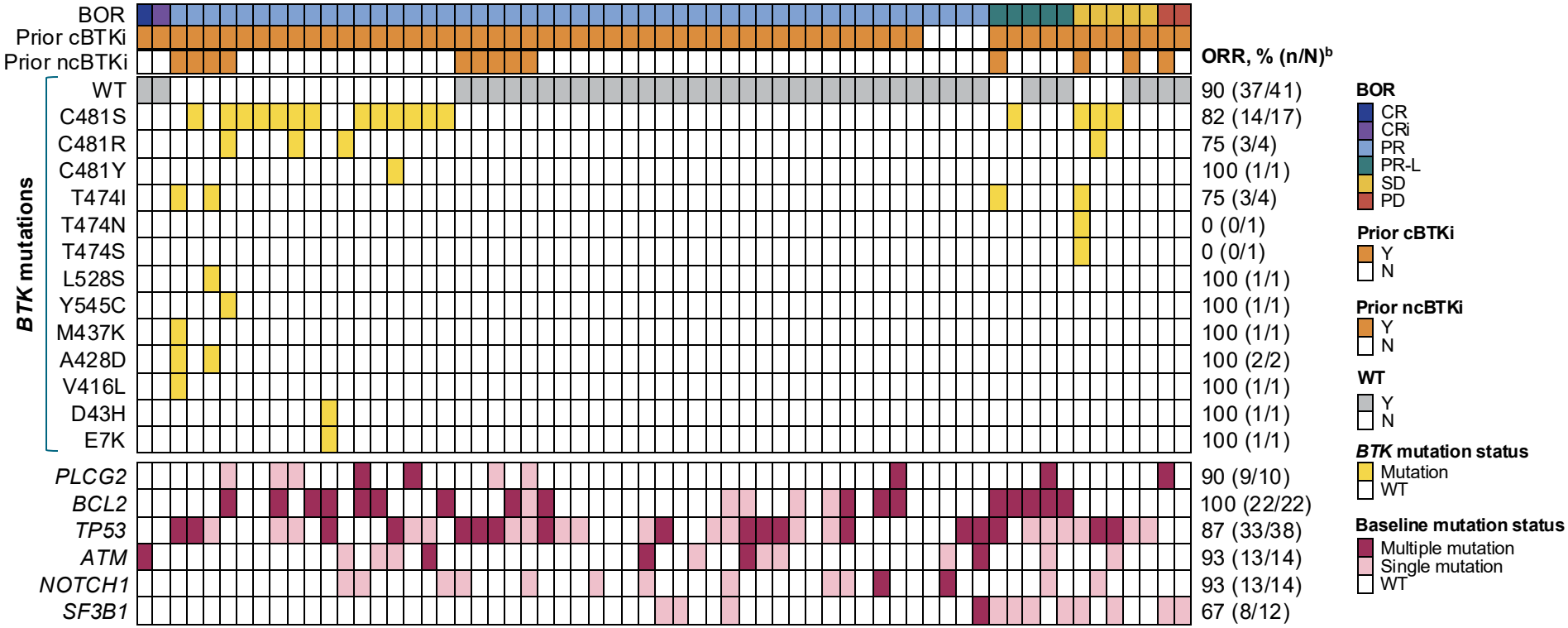
Durable PFS in heavily-pretreated patients across all dose levels in phase 1



Data cutoff: February 25, 2026.
PFS, progression-free survival.

Responses Occurred Regardless of Specific Mutations

Best overall response vs baseline mutation[a]

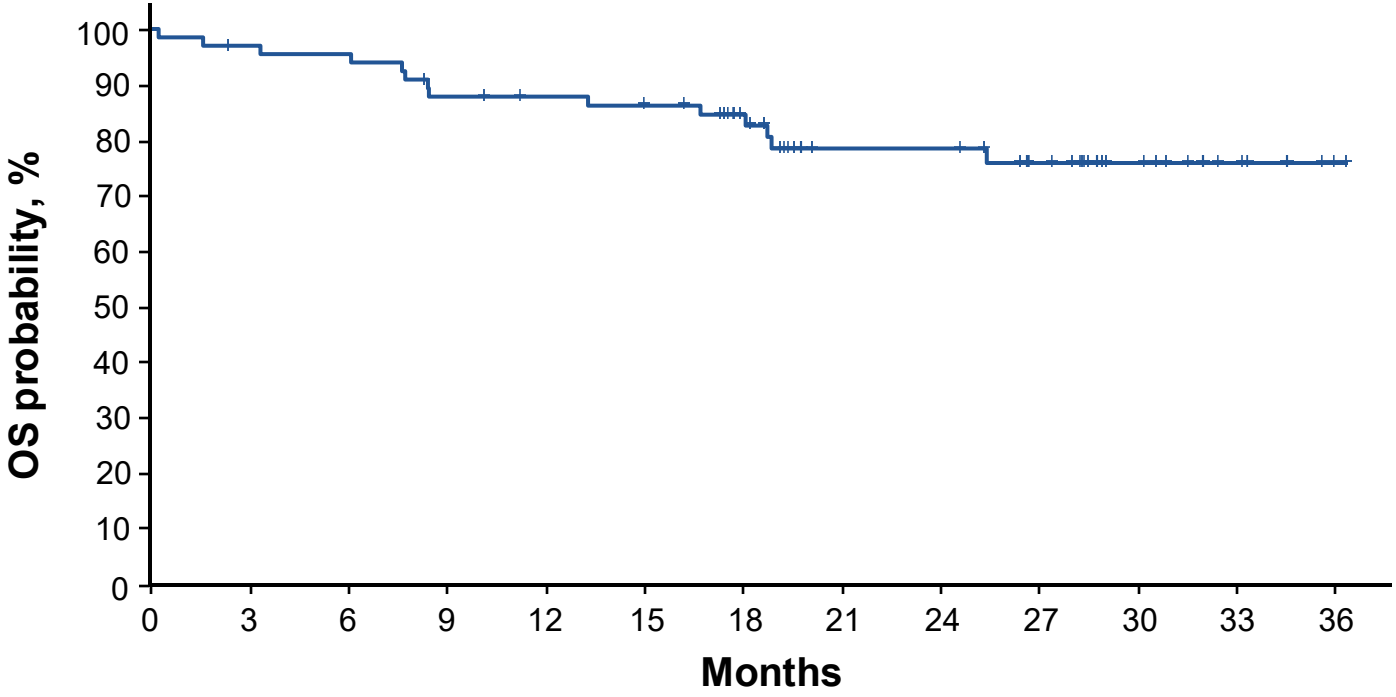


[a]Genomic mutations were centrally assessed by targeted next-generation sequencing. [b]Number of responders/number of patients with mutation.

BOR, best overall response; BTK, Bruton tyrosine kinase; cBTKi, covalent Bruton tyrosine kinase inhibitor; CR, complete response; CRi, complete response with incomplete marrow recovery; ncBTKi, noncovalent Bruton tyrosine kinase inhibitor; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; WT, wild-type.

Overall Survival

Favorable survival in heavily pretreated patients

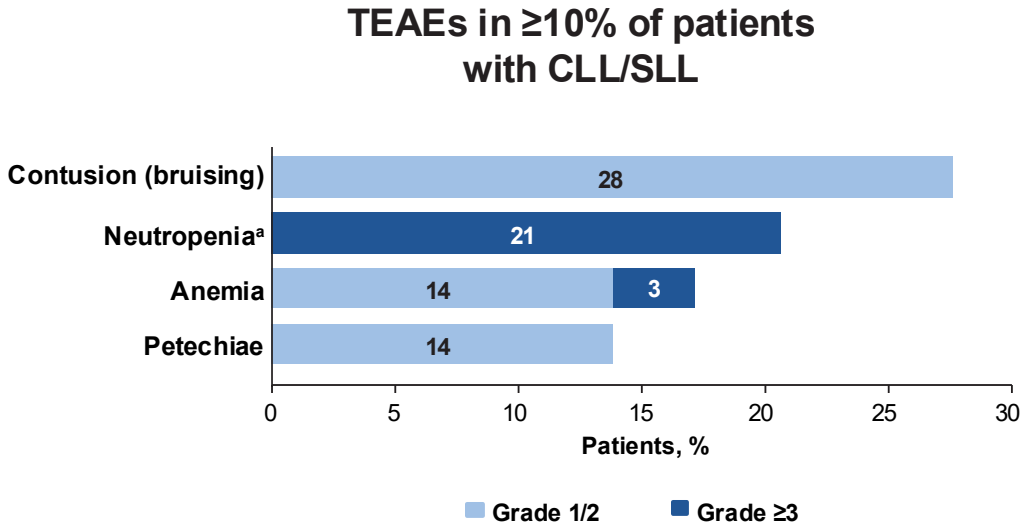


Data cutoff: February 25, 2026.

BTKi, Bruton tyrosine kinase inhibitor; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; OS, overall survival.

Separate Cohort 1F (BTKi–Naive Patients): Promising Safety and Efficacy

- 54 patients, including 29 with CLL/SLL (11 of them TN)
  - Median follow-up: 8.3 months
  - Median prior lines of treatment: 2 (range, 0-9)
- Safety
  - 33.3% had grade ≥3 TEAEs
  - No major hemorrhage, opportunistic infections (including invasive fungal infections), or febrile neutropenia
- Efficacy for CLL/SLL (n=22, n≤10 for other histologies)
  - ORR: 86.4%
  - No PFS events at 6 months



Mocanu et al. EHA 2026. Poster PS1693

Data cutoff: December 15, 2025.

[a]Neutropenia combines preferred terms *neutropenia* and *neutrophil count decreased.* The values of any-grade TEAEs have been calculated from individual grade 1/2 and grade ≥3 values rounded to the nearest whole number.

BTKi, Bruton tyrosine kinase inhibitor; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event; TN, treatment naive.

Conclusions

- The novel BTK degrader **tacabrutideg** (BGB-16673) demonstrated a **tolerable safety** profile, which was consistent and expected for patients with **R/R CLL/SLL** who received multiple prior lines of therapy.
  - No new safety signals were observed at a median duration of exposure of 18.2 months
  - As of the data cutoff, 50.7% of patients remained on treatment
- **Significant antitumor activity** in **heavily pretreated patients** and those with **high-risk features**
  - Response rates were high at 85.1% across all doses and 94.1% at RP2D (200 mg)
  - The ORR was 83.8% in CLL/SLL that was refractory to last cBTK inhibitor and last BCL2 inhibitor
  - Disease control was maintained as evidenced by a median PFS of 24.4 months with 25.4 months median study follow up
  - Favorable OS reported in heavily pretreated cohort with biological high-risk characteristics
- Favorable safety profile in BTKi–naive patients with promising response in patients with CLL/SLL
- **Tacabrutideg** is being evaluated in ongoing **phase 2 and 3** studies in patients with **R/R CLL/SLL**

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