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

P230

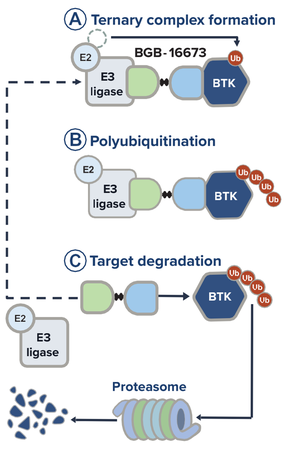
Damien Roos-Weil,[1] Meghan C. Thompson,[2] Ricardo D. Parrondo,[3] Anna Maria Frustaci,[4] John N. Allan,[5] Paolo Ghia,[6,7] Irina Mocanu,[8] Constantine S. Tam,[9] Judith Trotman,[10] Inhye E. Ahn,[11] Stephan Stilgenbauer,[12] Lydia Scarfo,[6,7] Kunthel By,[13] Shannon Fabre,[13] Daniel Persky,[13] Amit Agarwal,[13] John F. Seymour[14]

[1]Pitié-Salpêtrière Hospital, Paris, France; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Mayo Clinic - Jacksonville, Jacksonville, FL, USA; [4]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [5]Weill Cornell Medicine, New York, NY, USA; [6]Università Vita-Salute San Raffaele, Milano, Italy; [7]IRCCS Ospedale San Raffaele, Milano, Italy; [8]Institute of Oncology, ARENSIA Exploratory Medicine, Düsseldorf, Germany; [9]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [10]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [11]Dana-Farber Cancer Institute, Boston, MA, USA; [12]Ulm University, Ulm, Germany; [13]BeiGene USA, Inc, San Mateo, CA, USA; [14]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, VIC, Australia

INTRODUCTION

- Many patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) experience disease progression despite treatment with Bruton tyrosine kinase (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 (**Figure 1**)[4]
- In preclinical models, BGB-16673 degraded both wild-type and mutant BTK resistant to covalent BTK (cBTK) inhibitors (C481S, C481F, C481Y, L528W, T474I) and noncovalent BTK (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]
- Presented here are updated safety and efficacy data for patients with relapsed/refractory (R/R) CLL/SLL and preliminary efficacy data for patients with R/R Richter transformation (RT) from the phase 1 study, CaDAnCe-101

Figure 1. BGB-16673: A BTK-Targeted CDAC



Attributes and Potential Advantages of BGB-16673

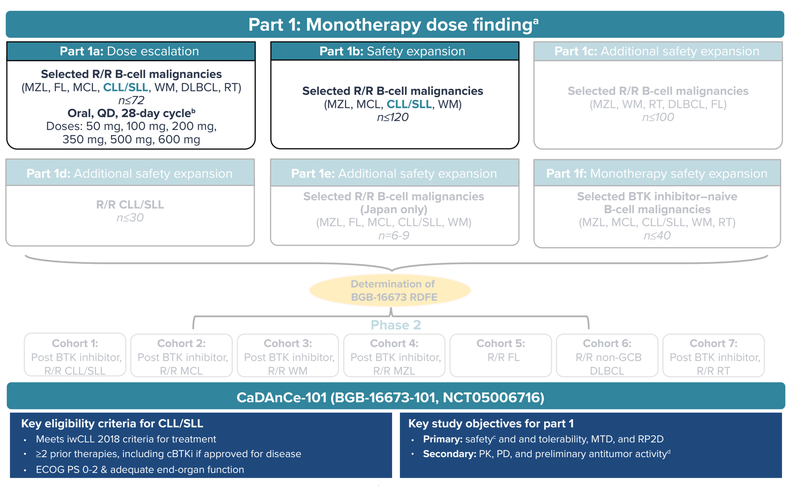
- Catalytic pharmacology that does not require sustained target binding
- Can interrupt formation of oncogenic protein complexes (scaffolding)
- Potential to overcome resistance mutations (eg, BTK C481S, C481F, C481Y, L528W, and V416L)
- Substantially reduced immunomodulatory drug activity; Aiolos and Ikaros are not significantly degraded

CDAC, chimeric degradation activating compound; ub, ubiquitin.

METHODS

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

Figure 2. CaDAnCe-101 Study Design



[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.
cBTK, covalent Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLT, dose-limiting toxicity; GCB, germinal center B cell; MTD, maximum tolerated dose; RT, Richter transformation.

RESULTS

- As of September 2, 2024, 60 patients with R/R CLL/SLL had received BGB-16673
- Patients were heavily pretreated, with a median of 4 (range, 2-10) prior lines of therapy, and had high-risk CLL features at study entry (**Table 1**)

Table 1. Baseline Patient Characteristics

	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)**
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)

[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.

Safety

- TEAEs led to death in 3 patients, none of which were treatment related (**Table 2**)
- One dose-limiting toxicity (DLT) occurred in the 200-mg cohort (grade 3 maculopapular rash; treatment continued after a 5-day hold)
- TEAEs in ≥10% of patients are shown in **Table 3**
- No atrial fibrillation or pancreatitis occurred
- Major hemorrhage occurred in 2 patients (3.3%; grade 1 subarachnoid hemorrhage [n=1] and grade 3 subdural hemorrhage [n=1])
- Febrile neutropenia occurred in 1 patient (1.7%; in the context of COVID-19 pneumonia and norovirus diarrhea)

Table 2. Overall Safety Summary

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

Median follow-up in safety-evaluable patients: 10.2 months (range, 0.3-26.4+).
TEAE, treatment-emergent AE.

Table 3. TEAEs in ≥10% of All Patients

	Total (N=60)	
Patients, n (%)	**All Grade**	**Grade ≥3**
Fatigue	18 (30.0)	1 (1.7)
Contusion (bruising)	17 (28.3)	0
Neutropenia[a]	15 (25.0)	13 (21.7)
Diarrhea	14 (23.3)	1 (1.7)
Anemia	11 (18.3)	0
Lipase increased[b]	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[c]	7 (11.7)	2 (3.3)
Amylase increased[b]	6 (10.0)	0
Nausea	6 (10.0)	0
Sinusitis	6 (10.0)	0

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

Antitumor Activity

- For 49 response-evaluable patients, the ORR was 77.6% (**Table 4** and **Figure 4**)
  - High ORRs were observed across various patient subgroups (**Table 5**)
  - Responses were observed regardless of specific mutations in key signaling molecules such as BTK and *TP53* and in patients with RT (**Figure 5**)

Table 4. Overall Response Rate by Dose

	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.

Table 5. Overall Response Rate by Subgroup

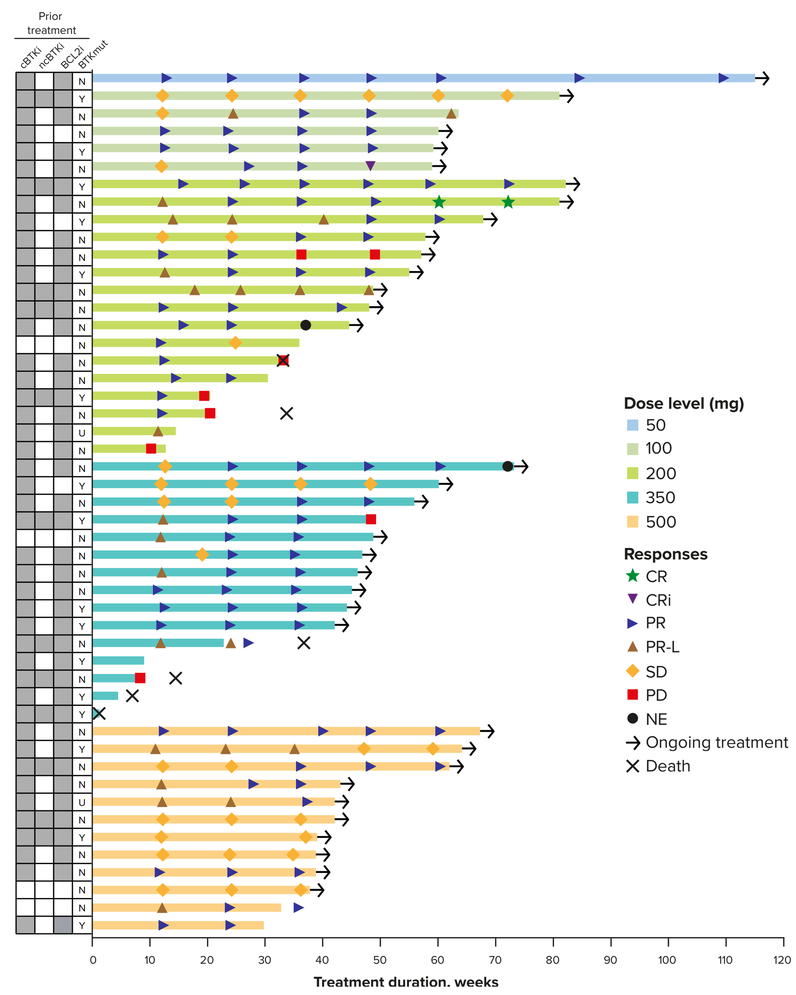
Characteristic, n/N with known status (%)	Total (N=49)
Double exposure (previously received cBTKi + BCL2i)	26/30 (86.7)
Triple exposure (previously received cBTKi + ncBTKi + BCL2i)	7/12 (58.3)
del(17p) and/or *TP53* mutation	23/31 (74.2)
Complex karyotype	11/15 (73.3)
BTK mutations	10/16 (62.5)
PLCG2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

BCL2i, BCL2 inhibitor; cBTKi, covalent BTK inhibitor; ncBTKi, non-covalent BTK inhibitor.

CONCLUSIONS

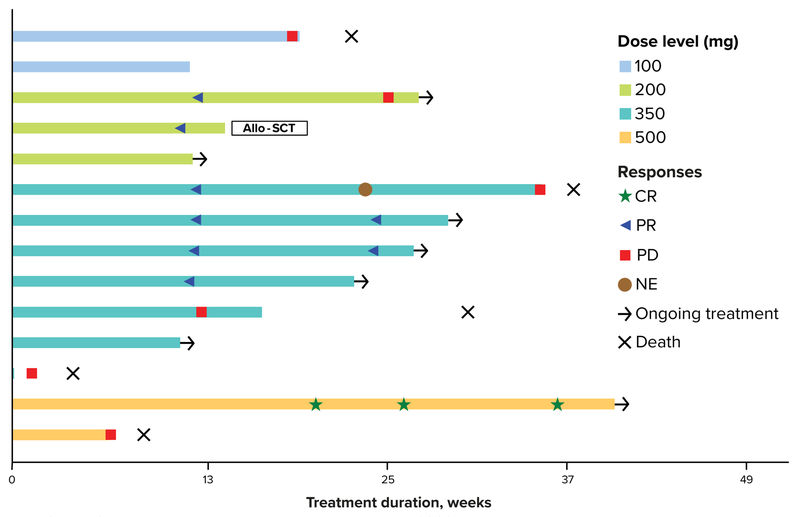
- In phase 1 of CaDAnCe-101, the novel BTK degrader BGB-16673 was safe and well tolerated in this heavily pretreated population of patients with R/R CLL/SLL
  - One DLT occurred, and the MTD was not reached
  - No atrial fibrillation was observed
- BGB-16673 had durable antitumor activity with a short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

Figure 4. Treatment Duration and Response



Median follow-up in efficacy-evaluable patients was 11.0 months (range, 0.3-26.4+). First response assessment after 12 weeks.
BCL2i, BCL2 inhibitor; cBTKi, covalent BTK inhibitor; CRi, complete response with incomplete marrow recovery; ncBTKi, non-covalent BTK inhibitor; NE, not evaluable; PR-L, partial response with lymphocytosis.

Figure 5. Responses in Patients With RT



Median follow-up for response-evaluable patients with RT was 5.7 months (range, 0.9-9.2+).
cBTKi, covalent BTK inhibitor; NE, not evaluable.

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, and Brazil

REFERENCES

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.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. They also thank Amber Lussier and Moto Takai for assistance in developing this presentation and Qiming Zhou from Bioinformatics for assistance on the high throughput data analysis. This study was sponsored by BeiGene, Ltd. Medical writing was provided by Brittany Gifford, PharmD, of Nucleus Global, an Inizio company, and supported by BeiGene.

DISCLOSURES

DR-W: Consulting or Advisory role: AbbVie, AstraZeneca, BeiGene, Janssen-Cilag, Lilly; Travel, accommodations, expenses: AbbVie, BeiGene, Janssen-Cilag. **MCT:** Honoraria: PeerView Medical Institute, Dava Oncology, eScientiq, Mashup Media LLC, Philips Group Oncology Communications, Intellisphere LLC/OncLive; Consulting or Advisory role: AbbVie, AstraZeneca, BeiGene, Janssen, Loxo Oncology at Lilly; Research funding: AbbVie, Adaptive Biotechnologies, AstraZeneca, BeiGene, GenMab, Nurix Therapeutics, Genentech; Travel support: Nurix Therapeutics, Genmab, Dava Oncology. **RDP:** : Honoraria: Sanofi Aventis, AstraZeneca, MJH Life Sciences, OncLive; Research funding: BMS, GSK. **AMF:** Honoraria and Consulting or advisory role: AbbVie, BeiGene, AstraZeneca, Janssen; Travel, accommodations, expenses: AbbVie, BeiGene, AstraZeneca. **JNA:** Consulting or advisory role: AbbVie, Adaptive Biotechnologies, ADC Therapeutics, AstraZeneca, BeiGene, Genentech, Janssen, Lilly, Merck, NeoGenomics, Pharmacyclics; Research funding: BeiGene, Celgene/BMS, Genentech; Speaker's bureau: AbbVie, BeiGene. **PG:** Consultant or advisory role and honoraria: AbbVie, AstraZeneca, BeiGene, BMS, Galapagos, Johson & Johnson, Lilly/Loxo Oncology, MSD, Roche. IM: No disclosure. **CST:** Honoraria: AbbVie, Janssen, BeiGene, AstraZeneca. **JT:** Research funding: BeiGene, BMS, Cellectar, Roche. **IEA:** Consulting or advisory role and Research funding: BeiGene. **SS:** Honoraria, consulting or advisory role, research funding, speakers bureau, and travel, accommodations, or expenses: AbbVie, Amgen, AstraZeneca, BeiGene, BMS, Gilead, GSK, Hoffmann-La Roche, Janssen, Lilly, Novartis, Sunesis. **LS:** Consulting or advisory role: AbbVie, AstraZeneca, BeiGene, Johnson & Johnson, Lilly, Merck; Travel, accommodations, expenses: AstraZeneca, BeiGene, Johnson & Johnson. **KB:** Employment and travel, accommodations, expenses: BeiGene. **SF:** Employment and may own stock: BeiGene; BMS; Advisory role, travel, accommodations, or expenses: BeiGene. **DP:** Employment and may own stock: BeiGene. **AA:** Employment and may own stock: BeiGene. **JFS:** Consultancy: Genor Bio, TG Therapeutics; Honoraria: AbbVie, AstraZeneca, BeiGene, BMS, Gilead, Janssen, Roche; Research funding: AbbVie, BMS, Roche; Speaker's bureau: AbbVie, AstraZeneca, BMS, Roche.

CORRESPONDENCE: Damien Roos-Weil, damien.roosweil@aphp.fr

Presented at the 45th SFH Annual Meeting; April 2-4, 2025; Paris, France
Data originally presented at the 66th ASH Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA. Abstract 885