

Preliminary Efficacy and Safety of the Bruton Tyrosine Kinase Degradar BGB-16673 in Patients With Relapsed/Refractory Richter Transformation: Results From the Ongoing Phase 1 CaDAnCe-101 Study

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CaDAnCe-101

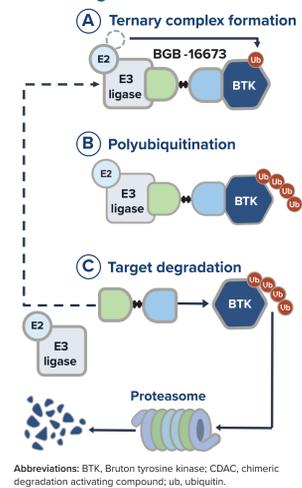
CONCLUSIONS

- In phase 1 of CaDAnCe-101, the BTK degrader BGB-16673 had a tolerable safety profile in heavily pretreated patients with R/R RT
 - Only three patients discontinued treatment due to TEAEs
- Promising efficacy was observed, including in patients with *BTK* and *TP53* mutations, and those previously exposed to BCL2 and ncBTK inhibitors, and anthracycline-based CIT
 - The ORR was 45.8% (11/24), including a CR rate of 12.5% (3/24), with responses lasting >6 months in heavily pretreated patients with R/R RT
 - Median time to first response was 2.8 months
- These data support further investigation of BGB-16673 clinical activity in patients with R/R RT

INTRODUCTION

- Richter transformation (RT) of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) to diffuse large B-cell lymphoma remains a pressing clinical challenge, with no established standard of care¹
- Existing therapies, such as chemoimmunotherapy (CIT) and Bruton tyrosine kinase (BTK) inhibitors ± checkpoint inhibitors, yield short-lived responses, with poor patient outcomes¹
- 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 regression² (Figure 1)
- By degrading BTK, BGB-16673 disrupts both inherent BTK catalytic activity and its separate protein scaffolding functions, in contrast to small molecule BTK inhibitors that temporarily block BTK catalytic activity alone^{3,4}
- The elimination of BTK by degradation may be effective against treatment-resistant BTK mutants that have been shown to limit the efficacy of current BTK inhibitors³
- In preclinical models, BGB-16673 degraded both wild-type BTK and mutant forms of BTK that have shown resistance to covalent and noncovalent BTK inhibitors; additionally, BGB-16673 showed central nervous system (CNS) penetration^{2,5}
- In a clinical study, BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue⁶
- Here, preliminary safety and efficacy results in patients with relapsed/refractory (R/R) RT in phase 1 of CaDAnCe-101 are presented

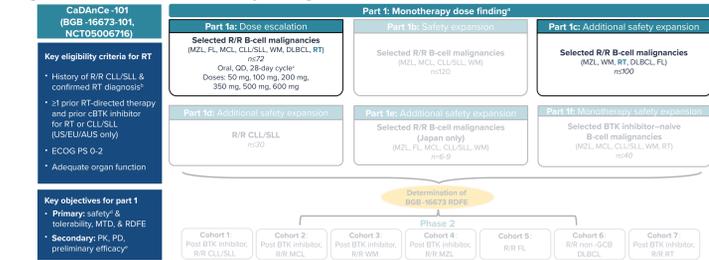
Figure 1. BGB-16673: A BTK-Targeted CDAC



METHODS

- 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 (Figure 2)

Figure 2. CaDAnCe-101 Study Design



*Data from gray portions of the figure are not included in this presentation. *Patients with progressive CLL/SLL who had a prior history of RT were included in the RT cohort. †Treatment was administered until progression, intolerance, or other criteria were met for treatment discontinuation. ‡Safety was assessed according to NCI-CTCAE v5.0. ††Response was assessed for RT per Lugano 2014 criteria after 12 weeks. ‡‡Abbreviations: BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; 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; 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.

RESULTS

- As of August 22, 2025, 24 patients with RT had received BGB-16673 (dose range, 100-500 mg)
- Patients were heavily pretreated, with a median of 3.5 (range, 1-11) prior lines of therapy for either CLL/SLL or RT (Table 1)
- All patients received CIT for RT prior to study enrollment (23/24 received anthracycline-based CIT)
- The median study follow-up was 71 months (range, 0.9-20.8 months)

Table 1. Baseline Patient Characteristics

	Total (N=24)
Age, median (range), years	67 (47-83)
Male, n (%)	15 (62.5)
ECOG PS, n (%)	
0	11 (45.8)
1	11 (45.8)
2	2 (8.3)
Bulky disease (LN >5 cm), n (%)	13 (54.2)
Elevated LDH, n (%)	16 (66.7)
Hemoglobin, median (range), g/L	106.5 (57.0-151.0)
Neutrophils, median (range), 10 ⁹ /L	3.2 (1.0-6.5)
Platelets, median (range), 10 ⁹ /L	148.0 (4.0-399.0)
Mutation status*	
TP53 mutation, n (%)	20 (83.3)
PLCG2 mutation, n (%)	7 (29.2)
BTK mutation, n (%)	5 (20.8)
Unmutated IGHV, n/N (%) ^b	10/11 (90.9)
No. of prior lines of therapy ^c , median (range)	3.5 (1-11)
Prior therapy, n (%)	
cBTK inhibitor	24 (100)
BCL2 inhibitor	14 (58.3)
ncBTK inhibitor ^d	5 (20.8)
Allogeneic or autologous stem cell transplant	4 (16.7)
CAR T-cell therapy	1 (4.2)
Chemoimmunotherapy	24 (100)
Anthracycline-based chemoimmunotherapy	23 (95.8)
Discontinued prior BTK inhibitor due to PD, n (%)	18 (75.0)

Data cutoff: August 22, 2025.

*Detected from either CLL or RT tissue. †Excludes patients with unknown status. ††Prior therapy could be for CLL/SLL or for RT. †††Of five patients with ncBTK inhibitor exposure, four were also exposed to a cBTK inhibitor.

Abbreviations: BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CAR, chimeric antigen receptor; cBTK, covalent Bruton tyrosine kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; LN, lymph node; ncBTK, noncovalent Bruton tyrosine kinase; PD, progressive disease; RT, Richter transformation.

Safety

- The overall safety summary is shown in Table 2
- The most common treatment-emergent adverse events (TEAEs) were neutropenia (37.5%) and nausea (20.8%) (Figure 3)
 - The most common grade ≥3 TEAEs were neutropenia (33.3%) and anemia (12.5%)
- Major hemorrhage (defined as grade ≥3, serious, or any CNS bleeding) occurred in one patient (grade 2 subdural hematoma)
- No cases of atrial fibrillation or febrile neutropenia occurred
- Three patients had TEAEs that led to treatment discontinuation (bacterial pneumonia, pneumonitis, and sepsis [1 each])
- Two patients had a TEAE that led to death: unknown death and pyrexia, both in the context of progressive disease (n=1 each); neither TEAE was considered to be treatment related

Table 2. TEAE Summary

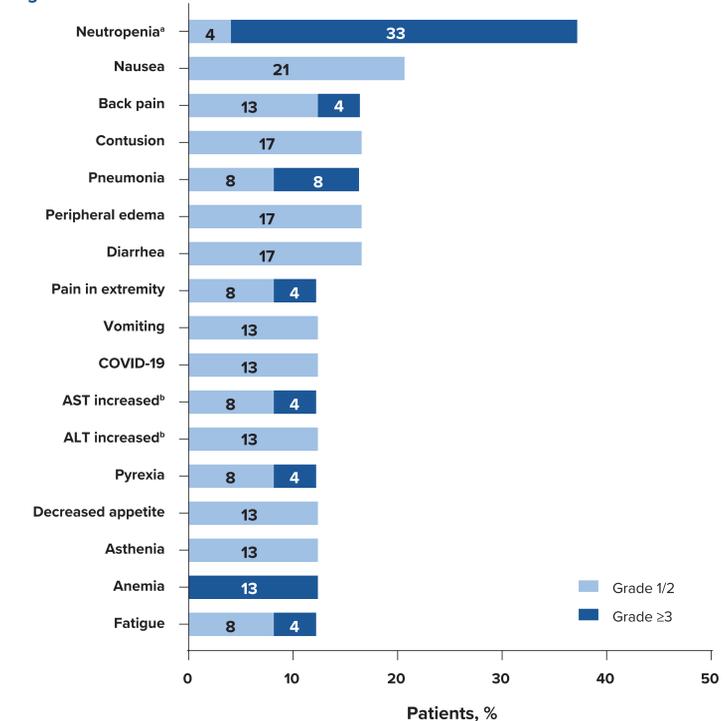
Patients, n (%)	Total (N=24)
Any TEAE	24 (100)
Any treatment-related	18 (75.0)
Grade ≥3	18 (75.0)
Treatment-related grade ≥3	11 (45.8)
Serious	10 (41.7)
Treatment-related serious	4 (16.7)
Leading to death ^a	2 (8.3)
Treatment-related leading to death	0
Leading to treatment discontinuation	3 (12.5)

Data cutoff: August 22, 2025. Median follow-up: 71 months (range, 0.9-20.8 months).

^aPyrexia and unknown death, both n=1 (note: both in the context of PD).

Abbreviations: PD, progressive disease; TEAE, treatment-emergent adverse event.

Figure 3. TEAEs in ≥10% of All Patients



^aNeutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. ^bAST and ALT increased were in the same patients.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Efficacy

- The overall response rate (ORR) was 45.8% (11/24), including a complete response (CR) rate of 12.5% (n=3) (Table 3)
- Responses were observed at all dose levels (ranging from 100 mg to 500 mg); in patients with prior exposure to a BCL2 or noncovalent BTK inhibitor; and regardless of specific baseline mutation status, including *BTK*, *TP53*, and *PLCG2* mutations (Table 3)
- Among the 11 patients who attained a response, five maintained a response for ≥6 months; of the remaining patients, three were censored and three experienced events prior to 6 months (Figure 4)
- One patient with an ongoing response discontinued treatment to undergo allogeneic stem cell transplant

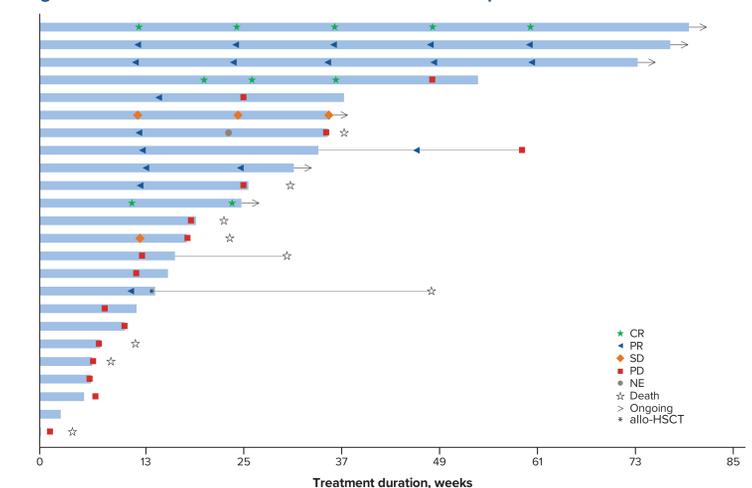
Table 3. Summary of Disease Responses in All Patients and by Mutation Status

	Total (N=24)
Best overall response, n (%)	
CR	3 (12.5)
PR	8 (33.3)
SD	2 (8.3)
PD	10 (41.7)
Discontinued prior to first assessment	1 (4.2)
ORR, n (%) ^a	11 (45.8)
Time to first response, median (range), months ^b	2.8 (2.6-4.6)
Characteristic, n/N with known status (%)	ORR
Previously received BCL2 inhibitor	7/14 (50.0)
Previously received ncBTK inhibitor	3/5 (60.0)
BTK mutations	4/5 (80.0)
TP53 mutations	9/20 (45.0)
PLCG2 mutations	2/7 (28.6) ^c
No BTK mutations post BTK inhibitor therapy	7/19 (36.8)

^aIncludes best overall response of PR or CR. ^bIn patients with a best overall response better than SD. ^cBoth patients with PLCG2 mutations who responded also had BTK mutations.

Abbreviations: BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CR, complete response; ncBTK, noncovalent Bruton tyrosine kinase; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 4. Swimlane Plot of Treatment Duration and Response Assessment



Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; BCL2i, B-cell lymphoma 2 inhibitor; BTKmut, Bruton tyrosine kinase mutation; cBTKi, covalent Bruton tyrosine kinase inhibitor; CR, complete response; ncBTKi, noncovalent Bruton tyrosine kinase inhibitor; NE, not evaluable; PD, progressive disease; PR, partial response; RT, Richter transformation; SD, stable disease.

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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ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeOne Medicines, Ltd. Medical writing was provided by Chris Kirik, PhD, and Brittany Gifford, PharmD, of Nucleus Global, an Inizio company, and supported by BeOne Medicines.