Preliminary Efficacy and Safety of the Bruton Tyrosine Kinase Degrader 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 care[1]
- Existing therapies, such as chemoimmunotherapy (CIT) and Bruton tyrosine kinase (BTK) inhibitors ± checkpoint inhibitors, yield short-lived responses, with poor patient outcomes[1]
- 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[2] (**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 inhibitors[3]
- 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 tissue[6]
- Here, preliminary safety and efficacy results in patients with relapsed/refractory (R/R) RT in phase 1 of CaDAnCe-101 are presented

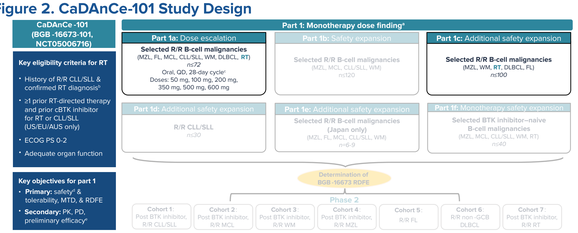
Figure 1 . BGB-16673: A BTK-Targeted CDAC

Abbreviations: BTK, Bruton tyrosine kinase; 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 adults 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]Patients with progressive CLL/SLL who had a prior history of RT were included in the RT cohort. [c]Treatment was administered until progression, intolerance, or other criteria were met for treatment discontinuation. [d]Safety was assessed according to NCI-CTCAE v5.0. [e]Response was assessed for RT per Lugano 2014 criteria after 12 weeks.[7]

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 7.1 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[a]	
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.
[a]Detected from either CLL or RT tissue. [b]Excludes patients with unknown status. [c]Prior therapy could be for CLL/SLL or for RT. [d]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

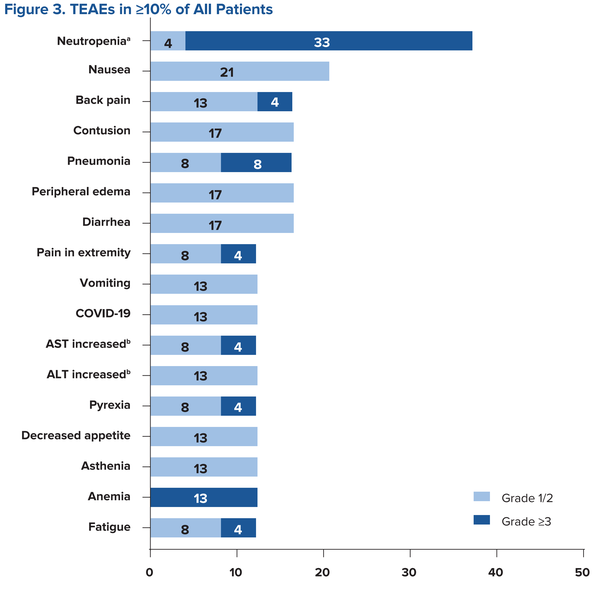
- The overall safety summary is shown in **Table 2**
- The most common treatment-emergent adverse events (TEAEs) were neutropenia (37.5%) and nausea (20.8%) (**Figure 3**)
  - The most common grade ≥3 TEAEs were neutropenia (33.3%) and anemia (12.5%)
- Major hemorrhage (defined as grade ≥3, serious, 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 serositis [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: 7.1 months (range, 0.9-20.8 months).
[a]Pyrexia 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



[a]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [b]AST and ALT increased were in the same patients.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Efficacy

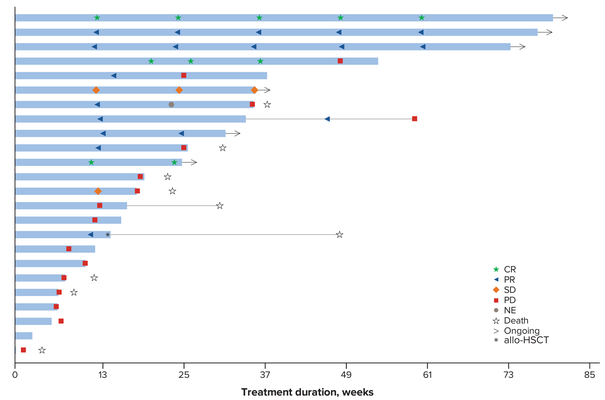
- The overall response rate (ORR) was 45.8% (11/24), including a complete response (CR) rate of 12.5% (n=3) (**Table 3**)
- Responses were observed at all dose levels (ranging from 100 mg to 500 mg); in patients with prior exposure to a BCL2 or noncovalent BTK inhibitor; and regardless of specific baseline 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)

[a]Includes best overall response of PR or CR. [b]In patients with a best overall response better than SD. [c]Both 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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