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Vorläufige Daten zur Wirksamkeit und Sicherheit des Bruton-Tyrosin-Kinase-Degraders BGB-16673 bei Patienten mit rezidivierter oder refraktärer CLL/SLL: Ergebnisse der Phase 1-Studie BGB-16673-101

CaDAnCe-101

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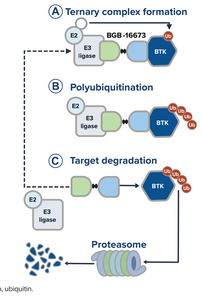
INTRODUCTION

- Many patients with CLL/SLL experience disease progression after BTK inhibitors[1-3]
- BGB-16673, a chimeric degradation activating compound, is a bivalent molecule comprising a BTK-binding moiety + linker + E3 ligase binder that induces BTK degradation via polyubiquitination[4] (**Figure 1**)
- In preclinical models, BGB-16673 degraded both wild-type and mutant BTK resistant to covalent and noncovalent BTK inhibitors, leading to tumor suppression[4,5]
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue in the first-in-human study[6]
- Here, the updated safety and efficacy results are presented from patients with R/R CLL/SLL in the ongoing CaDAnCe-101 study

Figure 1. BGB-16673: A Chimeric Degradation Activating Compound (CDAC)

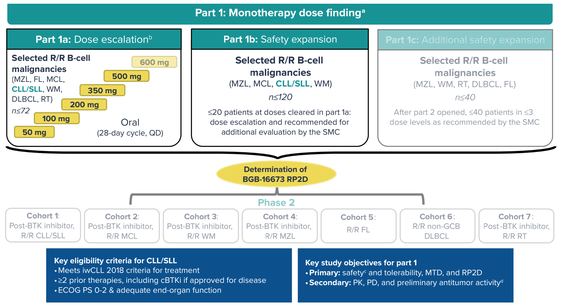


ub, ubiquitin.

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

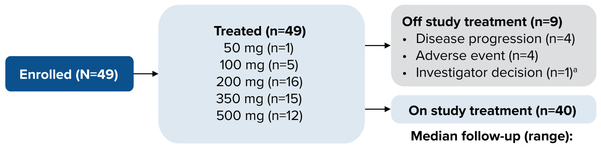


[a] Data from gray portions of figure are not included in this presentation. [b] Bayesian optimal interval design with 6 dose levels (50-600 mg orally QD). [c] Safety was assessed according to CTCAE v5.0 in all patients and iwCLL hematologic toxicity criteria in patients with CLL; DLTs were assessed during the first 4 weeks. [d] Response was assessed per iwCLL 2018 criteria after 12 weeks for patients with CLL.[7]
GCB, germinal center B-cell; RT, Richter transformation.

RESULTS

- As of February 14, 2024, 49 patients with R/R CLL/SLL enrolled in part 1a/1b and received BGB-16673 (**Figure 3**); 40 patients (82%) remained on treatment
- Of patients with available data, high-risk characteristics were prevalent, including: unmutated IGHV locus (82%), del(17p) or *TP53* mutation (60%), and complex karyotype (47%)

Figure 3. Patient Disposition



[a] Patient had ongoing low-grade arthralgia that did not otherwise meet the criteria for discontinuation.

Table 1. Baseline Characteristics

	Total (N=49)
Age, median (range), years	70 (50-91)
Male sex, n (%)	31 (63)
ECOG PS, n (%)	
1	19 (39)
2	1 (2)
CLL/SLL risk characteristics at study entry, n/N (%)	
Binet stage C	23/46 (50)
Unmutated IGHV	32/39 (82)
del(17p) or *TP53* mutation	28/47 (60)
Complex karyotype (≥3 abnormalities)	15/32 (47)
Mutation status, n/N (%)	
BTK mutation present	15/47 (32)
PLCG2 mutation present	6/47 (13)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	38 (78)
cBTK inhibitor	45 (92)
ncBTK inhibitor	11 (22)
BCL2 inhibitor	42 (86)
cBTK + BCL2 inhibitors	37 (76)
cBTK + ncBTK + BCL2 inhibitors	11 (22)
Discontinued BTK inhibitor due to PD, n/N (%)	40/45 (89)

cBTK, covalent BTK; ncBTK, noncovalent BTK.

- One DLT was reported (200-mg dose; grade 3 maculopapular rash)
- None of the 3 TEAEs that led to death were considered related to treatment by the investigator
- No cases of atrial fibrillation or grade ≥3 hypertension were reported

Table 2. Overall Safety Summary

Patients, n (%)	Total (N=49)
Any TEAE	47 (96)
Any treatment-related	30 (61)
Grade ≥3	27 (55)
Treatment-related grade ≥3	13 (27)
Serious	21 (43)
Treatment-related serious	6 (12)
Leading to death[a]	3 (6)
Treatment-related leading to death	0
Leading to treatment discontinuation[b]	6 (12)
Treatment-related leading to treatment discontinuation	1 (2)
Leading to treatment modification	18 (37)
Dose interruption	18 (37)
Dose reduction	3 (6)

[a] (1) Septic shock (350 mg); (2) aspergillosis (350 mg); (3) pneumonia (200 mg) in the context of PD. [b] (1) Aspergillosis and cerebral aspergillosis (350 mg); (2) general physical health deterioration (350 mg) in the context of PD; (3) septic shock (350 mg); (4) pneumonia (200 mg) in the context of PD; (5) subdural hemorrhage (350 mg); (6) thyroid carcinoma (200 mg).

Table 3. Most Common AEs (All Grade ≥10%)

	Total (N=49)	
Patients, n (%)	**All Grade**	**Grade ≥3**
Fatigue	16 (33)	1 (2)
Contusion	14 (29)	0
Anemia	11 (22)	1 (2)
Diarrhea	11 (22)	0
Neutropenia/neutrophil count decreased	11 (22)	10 (20)
Pneumonia	8 (16)	6 (12)
COVID-19	7 (14)	0
Cough	7 (14)	0
Dyspnea	7 (14)	0
Amylase increased[a]	6 (12)	0
Lipase increased[a]	6 (12)	1 (2)
Pyrexia	6 (12)	0
Thrombocytopenia/platelet count decreased	6 (12)	0
Arthralgia	5 (10)	0
Decreased appetite	5 (10)	0
Nausea	5 (10)	0

[a] All events were lab findings and were transient, mostly occurring during the first 1-3 cycles of treatment, with no clinical pancreatitis.

- The ORR was 72% (31/43) in response-evaluable patients with CLL/SLL (**Table 4**)
- The ORR for the 200-mg group was 88%, with 2 patients achieving CR
- The ORR was similar in patients who had previously received cBTK + BCL2 inhibitors (70%), del(17p) or *TP53* mutation (68%), and complex karyotype (67%)
- Responses have been observed in patients with C481S, T474I, and/or L528S BTK mutations, as well as patients with *PLCG2* mutations (**Figure 4**)

Table 4. Overall Response Rate

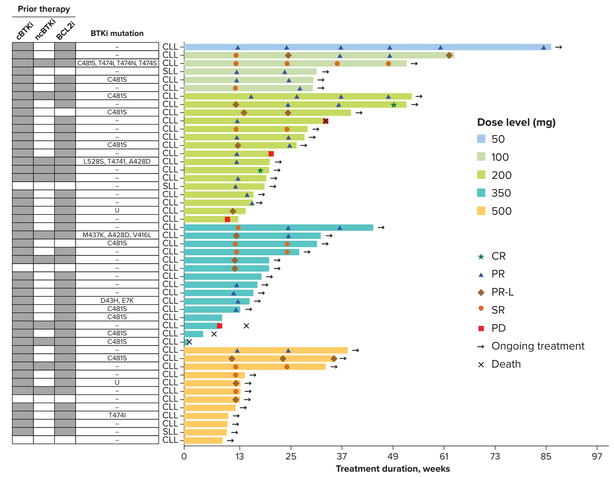
	50 mg (n=1)	100 mg (n=5)	200 mg (n=16)	350 mg (n=14)	500 mg (n=7)	Total (N=43)
Best overall response, n (%)[a]						
CR	0	0	2 (13)	0	0	**2 (5)**
PR	1 (100)	4 (80)	10 (63)	6 (43)	1 (14)	**22 (51)**
PR-L	0	0	2 (13)	2 (14)	3 (43)	**7 (16)**
SD	0	1 (20)	1 (6)	2 (14)	3 (43)	**7 (16)**
PD	0	0	1 (6)	1 (7)	0	**2 (5)**
Discontinued prior to first assessment	0	0	0	3 (21)	0	**3 (7)**
ORR, n (%)[b]	**1 (100)**	**4 (80)**	**14 (88)[c]**	**8 (57)**	**4 (57)**	**31 (72)**
Disease control rate, n (%)[d]	1 (100)	5 (100)	15 (94)	10 (71)	7 (100)	**38 (88)**
Follow-up time, median, months	19.8	7.2	6.3	3.9	3.3	**4.6[e]**
Time to first response, median (range), months[f]	2.9 (2.9-2.9)	4.2 (2.8-6.2)	2.8 (2.6-4.1)	2.8 (2.6-5.6)	2.8 (2.6-2.8)	**2.8 (2.6-6.2)**

[a] Percentages may not sum to 100 due to rounding. [b] Proportion of patients who achieved a best overall response of PR-L or better. [c] One additional patient reported response after the February 14, 2024 data cut, indicating a 94% ORR (15/16 patients) in the 200-mg dose group. [d] Proportion of patients who achieved a best overall response of SD or better. [e] Study follow-up enrolled set N=49. [f] Time to first qualifying response in patients with a best overall response better than SD.
PR-L, partial response with lymphocytosis.

CONCLUSIONS

- In results from this ongoing first-in-human study, the novel BTK degrader BGB-16673 showed a generally well tolerated safety profile in this heavily pretreated CLL population
  - One DLT was reported and MTD was not reached
  - No atrial fibrillation or grade ≥3 hypertension has been reported so far
- There was promising antitumor activity, including in patients with BTK inhibitor–resistant mutations and those previously exposed to cBTK inhibitors, ncBTK inhibitors, and BCL2 inhibitors
  - ORR was 72% (31/43) with an 88% ORR in the 200-mg group, including 2 CRs
  - Median time to first response was 2.8 months
  - Responses may continue to evolve as the study continues beyond the median 4.6-month follow-up
- A phase 2 cohort of patients with CLL/SLL exposed to both a cBTK inhibitor and BCL2 inhibitor is now enrolling
- These data support promising clinical activity of BGB-16673 in treatment of patients with CLL/SLL
- Enrollment for the CaDAnCe-101 study part 1c and phase 2 is ongoing at 90 of 115 planned study sites across the US, Canada, UK, France, Georgia, Germany, Italy, Moldova, Spain, Sweden, Turkey, Australia, South Korea, and Brazil

Figure 4. Treatment Duration and Response



BTK mutation status listed or was absent (-) or unknown (U).
PR-L, partial response with lymphocytosis.

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DISCLOSURES

BFE: Advisory board: Janssen, AbbVie, BeiGene, AstraZeneca, MSD, Lilly; Speakers bureau: Roche, AbbVie, BeiGene, AstraZeneca, MSD; Honoraria: Roche, AbbVie, BeiGene, AstraZeneca, MSD; Research funding/grants: Janssen, Gilead, Roche, AbbVie, BeiGene, AstraZeneca; Travel expenses: BeiGene; Data Safety Monitoring Board. **RDP:** Research funding: BMS, GSK; Honoraria: Sanofi Aventis, AstraZeneca, MJH Life Sciences, OncLive. **MCT:** Research funding: AbbVie, AstraZeneca, BeiGene, GenMab, Nurix Therapeutics, Genentech; Consulting: AbbVie, AstraZeneca, BeiGene, Janssen, Loxo Oncology; Honoraria: Dava Oncology, Philips Group Oncology Communications, MJH Life Sciences, Intellisphere LLC, Clinical Care Options; Travel: Genmab, Nurix Therapeutics, Genentech. **AMF:** Consulting or advisory role: AbbVie, BeiGene, AstraZeneca, Janssen; Travel, accommodations, expenses: AbbVie, BeiGene. **JNA:** Consulting or advisory role: AbbVie, Adaptive Biotechnologies, ADC Therapeutics, AstraZeneca, BeiGene, Genentech, Janssen, Lilly, NeoGenomics, Pharmacyclics; Research funding: BeiGene, Celgene/BMS, Genentech, Janssen, Pharmacyclics, Regeneron; Speakers bureau: AbbVie, BeiGene, Janssen, Pharmacyclics; Other relationship: Merck. **PG:** Honoraria: AbbVie, AstraZeneca, BeiGene, BMS, Janssen, Galapagos, Lilly/Loxo, MSD, Roche; Research funding: AbbVie, AstraZeneca, BMS, Janssen. **IV:** Nothing to disclose. **CST:** Research funding: Janssen, AbbVie, BeiGene; Honoraria: Janssen, AbbVie, BeiGene, Lilly, AstraZeneca. **JT:** Research funding: BeiGene, BMS, Cellectar, Roche. **MC:** Research support: BeiGene; Grants: AbbVie, Geron, Oncternal, AstraZeneca, Protagonist; Consulting fees: Janssen. **XC, KB, AA:** Employment and may own stock: BeiGene. **SF:** Employment and may own stock: BeiGene; BMS, Advisory role, travel, accommodations, or expenses: 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. **JFS:** Advisory role: AbbVie, AstraZeneca, BeiGene, BMS, Genor Bio, Gilead, Janssen, Roche; Research funding: AbbVie, BMS, Janssen, Roche. Speakers bureau: AbbVie, BMS, Roche; Consultant: TG Therapeutics.

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