A First-in-Human, Phase 1a/b, Dose-Escalation/Expansion Study of BG-68501, a Selective CDK2 Inhibitor, as Monotherapy or in Combination With Fulvestrant for Patients With *HR+/HER2–* Breast Cancer and Other Advanced Solid Tumors: First Disclosure of Clinical Data

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CONCLUSIONS

- BG-68501 demonstrated a manageable safety/tolerability profile, with no dose-limiting toxicities (DLTs) observed to date during ongoing dose escalation
- Extensively pretreated patients achieving partial response (PR) and stable disease (SD) with monotherapy, coupled with signs of pharmacodynamic responses and a tolerable safety profile, support continued assessment of BG-68501
- Dose escalation of BG-68501 is ongoing for both monotherapy, as well as in combination with fulvestrant
- The study is actively enrolling patients in 31 sites in the United States, Australia, China, Israel, Republic of Korea, Republic of Moldova, and New Zealand (NCT06257264)

INTRODUCTION

- Similar to cyclin-dependent kinase 4/6 (CDK4/6), CDK2 regulates the cell cycle transition from G1 to the S phase, through phosphorylation and subsequent inactivation of the retinoblastoma tumor suppressor protein, which then derepresses E2-factor-mediated transcription (**Figure 1**)[1]

Figure 1. CDK2 Forms a Complex With Cyclin E and Cyclin A to Regulate the G1/S and S/G2 Cell Cycle Transitions

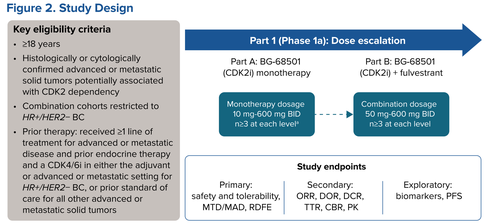
- Various genomic aberrations, such as *CCNE1* amplification, can upregulate CCNE1 protein levels, thus leading to increased CDK2 signaling in different tumors, such as high-grade serous ovarian cancer and uterine serous cancers[2]
  - Tumor types with higher prevalence of *CCNE1* amplification/cyclin E1 overexpression, such as ovarian cancer and other gynecological malignancies, are dependent on CDK2[3,4]
- Furthermore, cyclin E1/CDK2 upregulation has been linked with clinical resistance to the approved CDK4/6 inhibitors for patients with metastatic hormone receptor-positive/human epidermal growth factor receptor 2-negative breast cancer (*HR+/HER2–* BC)[5]
- BG-68501 is a highly potent CDK2 inhibitor with high CDK2 selectivity (~100x) vs other CDK family members[6]
- BG-68501, as a single-agent or combination therapy, is being investigated in a multicenter, open-label, dose escalation/expansion, first-in-human study in patients with advanced, metastatic, or unresectable solid tumors, including *HR+/HER2–* BC and platinum refractory or resistant ovarian cancer (PROC; NCT06257264)
- Here, we are presenting the safety/tolerability, pharmacokinetic (PK)/pharmacodynamic profiles, and preliminary antitumor activity of BG-68501 as monotherapy, as well as in combination with fulvestrant, from the ongoing, first-in-human, phase 1a dose escalation study

METHODS

Trial Design

- This phase 1, open-label, multicenter study consists of two parts, namely dose escalation and dose expansion; preliminary results from the dose-escalation part are presented here (**Figure 2**)
- During dose escalation, sequential cohorts will receive increasing doses of BG-68501 as monotherapy or in combination with fulvestrant

Figure 2. Study Design



The dose escalation will proceed according to the modified toxicity probability interval-2 method[7,8]
All antitumor endpoints will be assessed per RECIST v1.1 by investigator.
[a]n1 at 10 mg BID dosage.
Abbreviations: BID, twice per day; CBR, clinical benefit rate; DCR, disease control rate; DOR, duration of response; MAD, maximum administered dose; MTD, maximum tolerated dose; ORR, overall response rate; PFS, progression-free survival; RDFE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

RESULTS

Baseline Characteristics and Patient Disposition

- As of March 27, 2025, a total of 57 patients were enrolled
- The median (range) age was 62.0 (32.0-86.0) years, 19 (33.3%) patients had *HR+/HER2–* BC, 16 (28.1%) had ovarian cancer, 8 (14.0%) had endometrial cancer, and the remaining 13 (22.8%) patients had other tumor types (**Table 1**)
- This was a heavily pretreated cohort of patients with a median (range) of 4.0 (0-15) prior lines of therapy
  - Out of 19 patients with *HR+/HER2–* BC, all were previously treated with CDK4/6 inhibitors and endocrine therapy, 73.7% with chemotherapy, and 26.3% with antibody-drug conjugates, whereas out of 16 patients with ovarian cancer, 31.3% had received a PARP inhibitor and 43.8% a VEGF inhibitor
- Of the 13 patients with available local *CCNE1* amplification status, 8 patients had *CCNE1* amplification
- To date, 6 dose levels of BG-68501 monotherapy and 2 dose levels in combination with fulvestrant have been assessed
- The median (range) duration of exposure was 1.7 (0.2-8.3) months
- Median (range) study follow-up was 2.9 (0.3-11.3) months

Table 1. Baseline Characteristics (Safety Analysis Set)

	Part A BG-68501 monotherapy n=49	Part B BG-68501 + fulvestrant n=8	Total N=57
Median (range) age, years	63.0 (32.0-86.0)	60.0 (54.0-73.0)	62.0 (32.0-86.0)
Sex, n (%)			
Female	40 (81.6)	8 (100.0)	48 (84.2)
Male	9 (18.4)	0 (0.0)	9 (15.8)
Race, n (%)			
Asian	17 (34.7)	0 (0.0)	17 (29.8)
White	30 (61.2)	8 (100.0)	38 (66.7)
Other	2 (4.1)	0 (0.0)	2 (3.5)
Ethnicity, n (%)			
Hispanic or Latino	1 (2.0)	1 (12.5)	2 (3.5)
Not Hispanic or Latino	48 (98.0)	7 (87.5)	55 (96.5)
ECOG PS, n (%)			
0	18 (36.7)	5 (62.5)	23 (40.4)
1	31 (63.3)	3 (37.5)	34 (59.6)
Tumor type, n (%)			
HR+/HER2– BC	11 (22.4)	8 (100.0)	19 (33.3)
Endometrial	8 (16.3)	0 (0.0)	8 (14.0)
Ovarian[a]	16 (32.7)	0 (0.0)	16 (28.1)
Other[b]	14 (28.6)	0 (0.0)	14 (24.5)
Median (range) prior lines of therapy	4.0 (0-15)	3.0 (1-8)	4.0 (0-15)

[a]Ovarian cancer includes fallopian tube high-grade serous carcinoma (n=1), ovarian cancer besides PROC (n=3), and PROC (n=12). [b]Includes esophageal cancer (n=1), gastric cancer (n=1), small cell gallbladder cancer (n=2), prostate cancer (n=1), small cell lung cancer (n=4), triple-negative BC (n=5).
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; PROC, platinum refractory or resistant ovarian cancer.

Safety and Tolerability

- Treatment-emergent adverse events (TEAEs) occurred in 56 (98.2%) patients overall (**Table 2**)
  - The most common TEAEs were vomiting (63.2%), nausea (61.4%), and fatigue (26.3%), none of which were Grade ≥3 (**Table 3**)
- Grade ≥3 TEAEs were reported for 16 patients (28.1%)
- Serious TEAEs occurred in 12 patients (21.1%)
  - Dyspnea and intestinal obstruction were the only serious TEAEs to occur in ≥2 patients
- TEAEs leading to treatment discontinuation occurred in 2 patients at 25 mg BID dosage, 1 patient at 200 mg BID, and 1 patient at 250 mg BID
  - At 25 mg BID, 1 patient experienced Grade 1/2 diarrhea, nausea, and vomiting, and the other experienced Grade ≥3 platelet count increased and hypercalcemia. The 200 mg BID patient experienced Grade 1/2 hyperhidrosis, and the 250 mg BID patient experienced Grade 1/2 blood potassium decrease and hyperphosphatemia, and Grade ≥3 cholangitis
- No DLTs were observed
- There were no TEAEs leading to death

Table 2. Overall Safety Summary (Safety Analysis Set)

	Part A BG-68501 monotherapy							Part B BG-68501 + fulvestrant			Total N=57
	10 mg BID n=2	25 mg BID n=13	50 mg BID n=10	100 mg BID n=10	200 mg BID n=8	250 mg BID n=6	Subtotal n=49	50 mg BID n=4	100 mg BID n=4	Subtotal n=8	
Patients with any TEAE, n (%)	2 (100.0)	13 (100.0)	10 (100.0)	10 (100.0)	8 (100.0)	5 (83.3)	48 (98.0)	4 (100.0)	4 (100.0)	8 (100.0)	56 (98.2)
Grade ≥3	1 (50.0)	6 (46.2)	2 (20.0)	2 (20.0)	2 (25.0)	3 (50.0)	16 (32.7)	0 (0.0)	0 (0.0)	0 (0.0)	16 (28.1)
Serious	1 (50.0)	4 (30.8)	2 (20.0)	2 (20.0)	1 (12.5)	2 (33.3)	12 (24.5)	0 (0.0)	0 (0.0)	0 (0.0)	12 (21.1)
Leading to treatment discontinuation	0 (0.0)	2 (15.4)	0 (0.0)	0 (0.0)	1 (12.5)	1 (16.7)	4 (8.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (7.0)
Patients with any treatment-related TEAE, n (%)	1 (50.0)	9 (69.2)	6 (60.0)	10 (100.0)	7 (87.5)	5 (83.3)	38 (77.6)	3 (75.0)	3 (75.0)	6 (75.0)	44 (77.2)
Grade ≥3	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	2 (4.1)[a]	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.5)
Serious	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to treatment discontinuation	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)

[a]One Grade 3 anemia and one Grade 3 neutropenia.
A TEAE is defined as an AE that had onset or increase in severity level date on or after the date of the first dose of study drug and up to 30 days after the last dose of study drug(s) or the initiation of new anti-cancer therapy, whichever is earlier.
Treatment-related TEAEs include those events considered by the investigator to be related or with missing assessment of the causal relationship.
AEs were classified based on MedDRA and were graded for severity using NCI-CTCAE v5.0.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE v5.0, National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0.

Table 3. Most Common TEAEs in >10% of Total Patients (Safety Analysis Set)

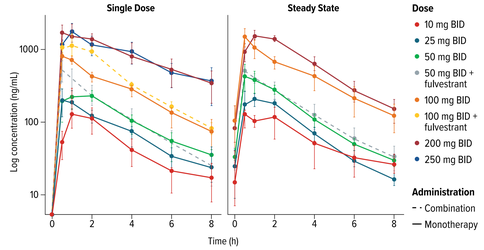
	Part A BG-68501 monotherapy							Part B BG-68501 + fulvestrant			Total N=57
	10 mg BID n=2	25 mg BID n=13	50 mg BID n=10	100 mg BID n=10	200 mg BID n=8	250 mg BID n=6	Subtotal n=49	50 mg BID n=4	100 mg BID n=4	Subtotal n=8	
Vomiting	1 (50.0)	6 (46.2)	3 (30.0)	9 (90.0)	6 (75.0)	5 (83.3)	30 (61.2)	2 (50.0)	4 (100.0)	6 (75.0)	36 (63.2)
Nausea	1 (50.0)	6 (46.2)	6 (60.0)	6 (60.0)	6 (75.0)	5 (83.3)	30 (61.2)	2 (50.0)	3 (75.0)	5 (62.5)	35 (61.4)
Fatigue	1 (50.0)	2 (15.4)	2 (20.0)	4 (40.0)	3 (37.5)	0 (0.0)	12 (24.5)	1 (25.0)	2 (50.0)	3 (37.5)	15 (26.3)
Anemia	0 (0.0)	4 (30.8)	4 (40.0)	0 (0.0)	1 (12.5)	2 (33.3)	11 (22.4)	0 (0.0)	0 (0.0)	0 (0.0)	11 (19.3)
Constipation	0 (0.0)	1 (7.7)	3 (30.0)	0 (0.0)	2 (25.0)	3 (50.0)	9 (18.4)	1 (25.0)	0 (0.0)	1 (12.5)	10 (17.5)
Diarrhea	1 (50.0)	1 (7.7)	1 (10.0)	1 (10.0)	1 (12.5)	0 (0.0)	5 (10.2)	0 (0.0)	2 (50.0)	2 (25.0)	7 (12.3)
Headache	0 (0.0)	1 (7.7)	0 (0.0)	2 (20.0)	2 (25.0)	0 (0.0)	5 (10.2)	0 (0.0)	1 (25.0)	1 (12.5)	6 (10.5)

Adverse events were classified based on MedDRA and graded for severity using NCI-CTCAE v5.0.
Patients with multiple events for a given preferred term were counted once at the preferred term level.

PK

- BG-68501 is absorbed rapidly after oral administration with a median time to peak concentration of 0.75 hours (**Figure 3**)
- There was no obvious difference observed in PK between BG-68501 monotherapy and fulvestrant combination
- BG-68501 exposures increased approximately dose proportionally in the dose range evaluated

Figure 3. PK Profiles of BG-68501 Monotherapy and Combination Therapy With Fulvestrant

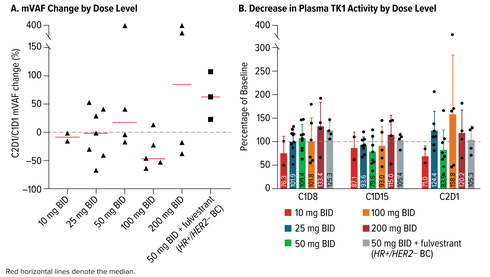


Abbreviations: h, hour.

Pharmacodynamics

- A decrease in circulating tumor DNA mean variant allele frequency (mVAF) was observed at 100 mg BID (**Figure 4A**)
- Moderate/minimal inhibition of TK1 activity in plasma was detected at all doses (**Figure 4B**)

Figure 4 . Pharmacodynamics



Red horizontal lines denote the median.
Abbreviations: C, cycle; D, day; TK1, thymidine kinase 1.

Antitumor Activity

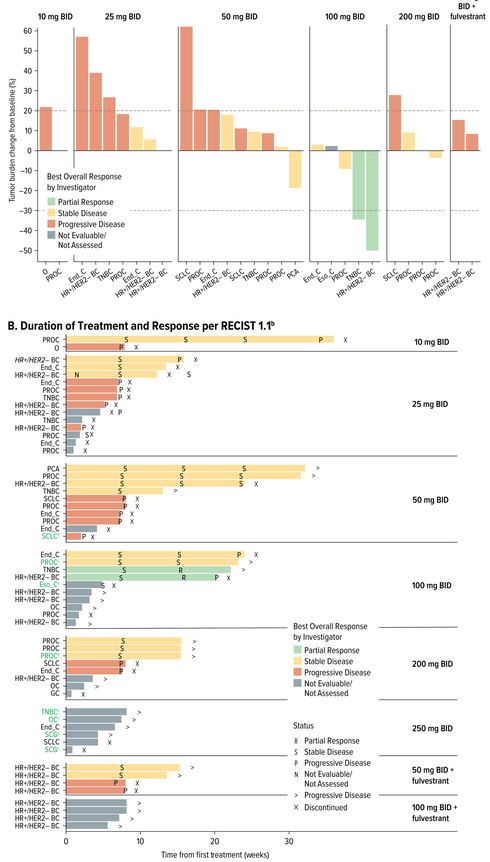
- Of the 37 efficacy-evaluable patients (all from Part A), 2 extensively pretreated patients with BC experienced unconfirmed PR, 15 patients had SD, 15 patients had progressive disease (PD), and 5 patients were not evaluable/not assessed (NE/NA; **Table 4**; **Figure 5**)
  - Of the 2 patients with PR, 1 was ongoing at time of data cutoff and the other had discontinued treatment (**Figure 5B**)

Table 4. Antitumor Activity (Efficacy Evaluable Set)

	Part A BG-68501 monotherapy						Part B BG-68501 + fulvestrant	Total N=37
	10 mg BID n=2	25 mg BID n=11	50 mg BID n=10	100 mg BID n=5	200 mg BID n=5	Subtotal n=33	50 mg BID n=4	
ORR, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	2 (6.1)	0 (0.0)	2 (5.4)
95% CI	0.0, 84.2	0.0, 28.5	0.0, 30.8	5.3, 85.3	0.0, 52.2	0.7, 20.2	0.0, 60.2	0.7, 18.2
BOR, n (%)								
PR	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	2 (6.1)	0 (0.0)	2 (5.4)
SD	1 (50.0)	3 (27.3)	4 (40.0)	2 (40.0)	3 (60.0)	13 (39.4)	2 (50.0)	15 (40.5)
PD	1 (50.0)	5 (45.5)	5 (50.0)	0 (0.0)	2 (40.0)	13 (39.4)	2 (50.0)	15 (40.5)
NE/NA	0 (0.0)	3 (27.3)	1 (10.0)	1 (20.0)	0 (0.0)	5 (15.2)	0 (0.0)	5 (13.5)
CBR, n (%)	1 (50.0)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	3 (9.1)	0 (0.0)	3 (8.1)
95% CI	1.3, 98.7	0.0, 28.5	0.0, 30.8	5.3, 85.3	0.0, 52.2	1.9, 24.3	0.0, 60.2	1.7, 21.9
DCR, n (%)	1 (50.0)	3 (27.3)	4 (40.0)	4 (80.0)	3 (60.0)	15 (45.5)	2 (50.0)	17 (45.9)
95% CI	1.3, 98.7	6.0, 61.0	12.2, 73.8	28.4, 99.5	14.7, 94.7	28.1, 63.6	6.8, 93.2	29.5, 63.1

Responses are unconfirmed
The 95% CI was estimated using the Clopper–Pearson method. CBR was defined as the proportion of patients who have CR, PR, or durable SD of ≥24 weeks in duration. DCR was defined as the proportion of patients who have CR, PR, or SD.
Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response.

Figure 5. Response: Part A BG-68501 Monotherapy and Part B BG-68501 + Fulvestrant



Response is unconfirmed.
[a]This plot shows post-baseline tumor assessments excluding patients without target lesions up to the initiation of new anti-cancer therapy or the first PD in the efficacy-evaluable population; [b]Safety population; [c]Patients with confirmed *CCNE1* amplification.
Abbreviations: End_C, endometrial cancer; Eso_C, esophageal cancer; GC, gastric cancer; O, other; fallopian tube high grade serous; OC, ovarian cancer (besides PROC); PCA, prostate cancer; SCG, small cell gallbladder cancer; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer.

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DISCLOSURES

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