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First Disclosure of Frontline Treatment With the Selective CDK4 Inhibitor BGB-43395 in Combination With Letrozole for Metastatic HR+/HER2− Breast Cancer: A Phase 1 Safety Expansion

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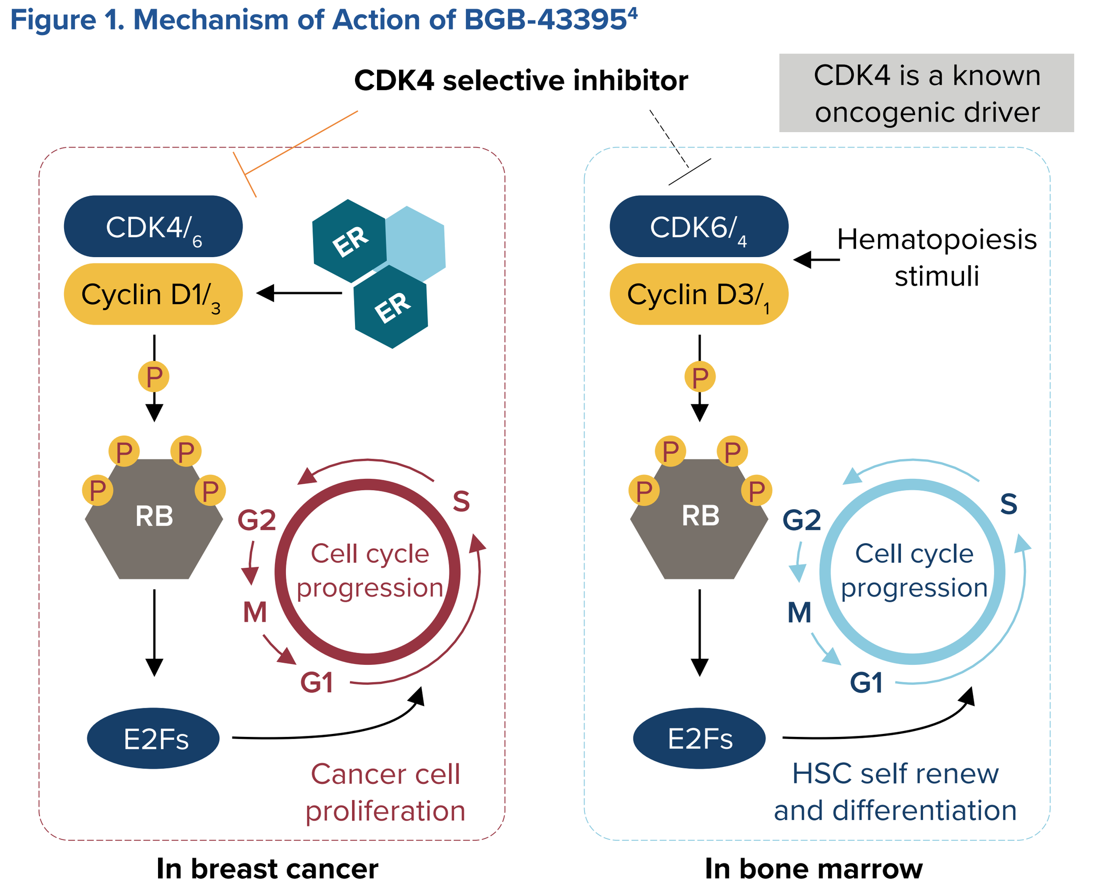
CONCLUSIONS

- BGB-43395 is a novel CDK4 inhibitor with high potency and selectivity for tumors with high CDK4 dependency, with the potential to minimize off-target toxicity
- BGB-43395, in combination with letrozole, demonstrated a favorable risk-benefit profile as frontline (1L) treatment for HR+/HER2− breast cancer; BGB-43395 400 mg BID was chosen as the recommended phase 3 development dose (RP3D)
  - Notably low rates and grades of hematologic toxicities; there were no grade ≥3 hematologic events at the RP3D
  - Gastrointestinal (GI) toxicity was manageable
  - No treatment-related adverse event (TRAE) led to discontinuation of study treatment at RP3D
  - Antitumor activity in 1L treatment of patients with advanced HR+/HER2− breast cancer was promising
- In an additional interim study, GI toxicity was reduced by administering BGB-43395 RP3D with food vs without food
  - Meaningful reductions of all grade treatment-related GI toxicities during the first 2 cycles were observed
  - Lower rates of grade 1 GI toxicities and no grade ≥2 GI events
- KANDELA-302 (NCT07492641), an open-label, randomized, multicenter phase 3 study, will evaluate the efficacy and safety of BGB-43395 400 mg BID + letrozole vs CDK4/6i (investigator's choice of abemaciclib, palbociclib, or ribociclib) + letrozole as 1L therapy in patients with HR+/HER2− advanced/metastatic breast cancer

INTRODUCTION

- Cyclin-dependent kinase 4 (CDK4), in complex with cyclin D, plays a critical role in regulating the G1-to-S phase transition of the cell cycle by phosphorylating the Rb protein and enabling release of E2F transcription factors, a pathway frequently dysregulated in HR+/HER2− breast cancer[1]
- Targeting CDK4/6 has become an effective therapeutic strategy, with inhibitors such as palbociclib, ribociclib, and abemaciclib approved in combination with endocrine therapy (eg, letrozole or fulvestrant) for patients with HR+/HER2− advanced breast cancer and high-risk early breast cancer[2,3]
  - However, acquired resistance and treatment-limiting toxicities highlight the need for more selective and potent CDK4 inhibitors with improved tolerability to improve clinical outcomes
- BGB-43395 is a potent, selective, and orally bioavailable CDK4 inhibitor that demonstrates strong selectivity for CDK4 over CDK6 (**Figure 1**)

Figure 1. Mechanism of Action of BGB-43395[4]



Selectively targeting CDK4, which drives cancer cell progression, allows for better coverage of CDK4 than CDK4/6i

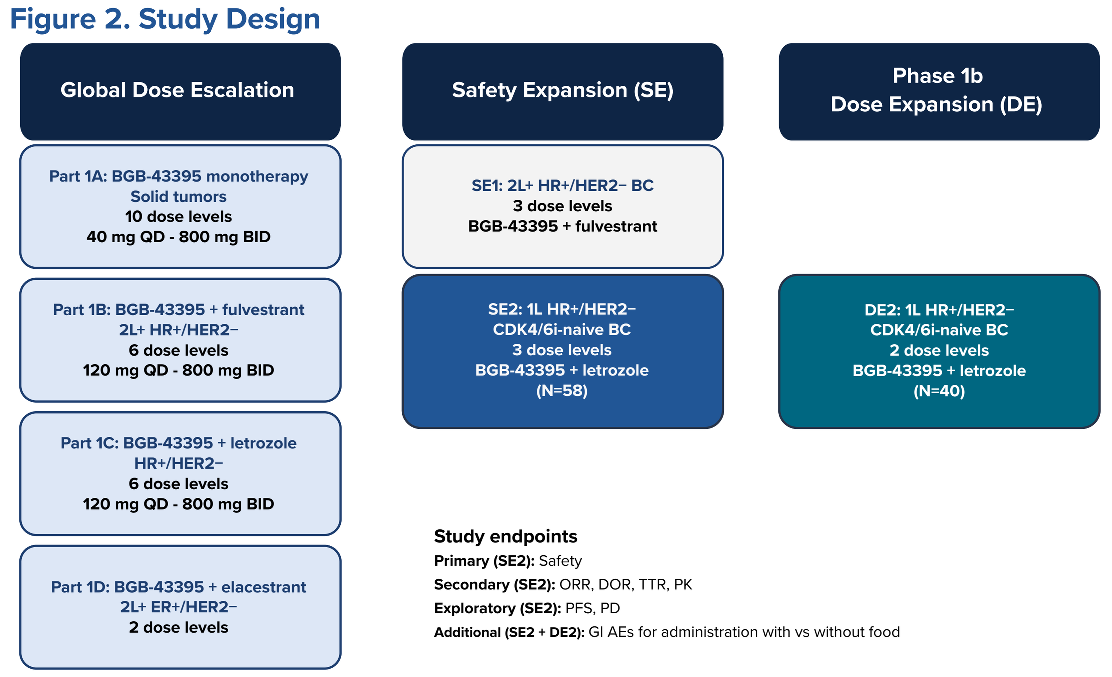
Abbreviations: BID, twice CDK, cyclin-dependent kinase; E2F, early 2 factor (transcription factor); ER, estrogen receptor; HSC, hematopoietic stem cell; RB, retinoblastoma.

- This is the first disclosure of data for BGB-43395 in combination with letrozole in the 1L treatment of patients with advanced or metastatic HR+/HER2− breast cancer (Safety Expansion Cohort 2 [SE2])
  - We also present data from an evaluation of the effect of administration of BGB-43395 with vs without food (pooled data from SE2 and Dose Expansion Cohort 2 [DE2])

METHODS

- The Phase 1a/1b BGB-43395-101 (NCT06120283) first-in-human open-label multicenter study has dose-escalation, optimization, and expansion components (**Figure 2**)
  - BGB-43395 was administered orally as monotherapy (for solid tumors with known CDK4 dependency) or in combination with endocrine therapy (for HR+/HER2− breast cancer)

Figure 2. Study Design



Abbreviations: BID, twice AE, adverse events; BC, breast cancer; BID, twice per day; DOR, duration of response; GI, gastrointestinal; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; TTR, time to response.

Key Eligibility Criteria (SE2 and DE2)

- Adults with advanced or metastatic HR+/HER2− breast cancer with no untreated or uncontrolled brain metastases
- No prior systemic therapies in the advanced or metastatic setting
- Use of GnRH agonists required for premenopausal females
- Other inclusion criteria included measurable disease per RECIST v1.1 and ECOG performance status ≤1

RESULTS

- As of April 30, 2026, 58 patients in cohort SE2 received study treatment (BGB-43395 dose: 240 mg n=19; 400 mg n=19; 600 mg n=20)
  - Median study follow-up was 12.5 (range, 3.1-15.2) months, 12.4 (range, 8.0-15.0) months, and 10.8 (range, 3.2-12.9) months for the 240 mg, 400 mg, and 600 mg dose groups, respectively
- Baseline characteristics were generally balanced between dose arms and cohorts (**Table 1**)

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	SE2 BGB-43395 240 mg BID + letrozole (n=19)	SE2 BGB-43395 400 mg BID + letrozole (n=19)	SE2 BGB-43395 600 mg BID + letrozole (n=20)	DE2 BGB-43395 400 mg BID + letrozole (N=20)
Median (range) age, years	43 (32-74)	61 (33-76)	50 (31-73)	62.5 (34-75)
Sex, n (%)				
Female	18 (94.7)	19 (100)	20 (100)	20 (100)
Male	1 (5.3)	0	0	0
Race, n (%)				
Asian	3 (15.8)	2 (10.5)	3 (15.0)	8 (40.0)
Black or African American	0	2 (10.5)	3 (15.0)	5 (25.0)
White	8 (42.1)	9 (47.4)	10 (50.0)	6 (30.0)
Multiple	0	3 (15.8)	0	0
Other	8 (42.1)	3 (15.8)	4 (20.0)	1 (5.0)
ECOG PS, n (%)				
0	14 (73.7)	10 (52.6)	10 (50.0)	8 (40.0)
1	5 (26.3)	9 (47.4)	10 (50.0)	12 (60.0)
Median (range) time from initial diagnosis of disease to first dose, years	0.36 (0.1-27.2)	0.40 (0.1-19.1)	0.60 (0.1-25.3)	0.28 (0.1-21.8)
De novo disease, n (%)	16 (84.2)	11 (57.9)	14 (70.0)	14 (70.0)
Visceral metastases, n (%)	10 (52.6)	15 (78.9)	18 (90.0)	13 (65.0)
Country				
Brazil	14 (73.7)	17 (89.5)	17 (85.0)	12 (60.0)
Malaysia	3 (15.8)	2 (10.5)	1 (5.0)	8 (40.0)
Republic of Moldova	2 (10.5)	0	1 (5.0)	0
Thailand	0	0	1 (5.0)	0

Abbreviations: BID, twice per day; DE2, dose expansion cohort 2; ECOG PS, Eastern Cooperative Oncology Group performance score; SE2, safety expansion cohort 2.

Safety Outcomes

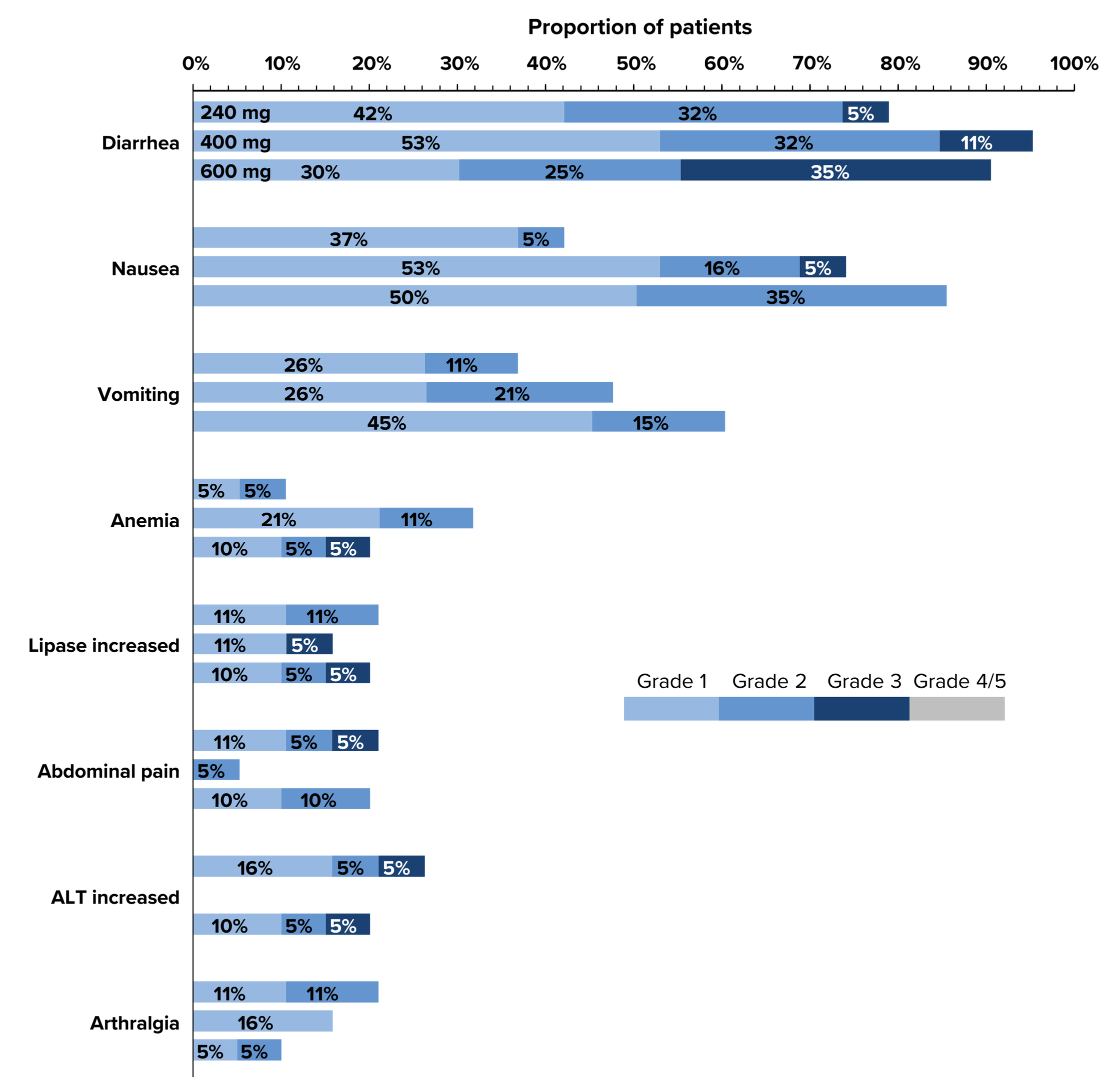
- The overall toxicity profile of BGB-43395 was manageable across 240 mg and 400 mg BID arms, where the majority of treatment-emergent adverse events (TEAE) were grade 1/2 (there were 3 grade 4 events [bilirubin conjugated increased, gamma-glutamyltransferase increased, and urinary tract infection] and 1 grade 5 pancreaticobiliary carcinoma; not treatment related) (**Table 2**)
- Rates of grade ≥3 TEAEs and TRAEs were higher for the BGB-43395 600 mg BID + letrozole arm
- The most common TRAEs were mostly grade 1/2 across all dose levels (**Figure 3**)

Table 2. Summary of Safety

Parameter, n (%)	BGB-43395 240 mg BID + letrozole (n=19)	BGB-43395 400 mg BID + letrozole (n=19)	BGB-43395 600 mg BID + letrozole (n=20)
Patient with any TEAE	18 (94.7)	19 (100)	20 (100)
Treatment related	17 (89.5)	19 (100)	20 (100)
Related to BGB-43395	17 (89.5)	19 (100)	20 (100)
Related to letrozole	8 (42.1)	10 (52.6)	11 (55.0)
Grade ≥3 TEAE	8 (42.1)	7 (36.8)	14 (70.0)
Related to BGB-43395	6 (31.6)	4 (21.1)	14 (70.0)
Serious TEAE	3 (15.8)	3 (15.8)	4 (20.0)
Related to BGB-43395	2 (10.5)	1 (5.3)	4 (20.0)
TEAE leading to death	0	1 (5.3)	0
Treatment related	0	0	0
TEAE leading to treatment discontinuation	1 (5.3)[a]	1 (5.3)[b]	1 (5.0)[c]
Related to BGB-43395	1 (5.3)	0	1 (5.0)
TEAE leading to treatment modification	7 (36.8)	10 (52.6)	16 (80.0)
TEAE leading to BGB-43395 modification	7 (36.8)	10 (52.6)	16 (80.0)
Dose interruption	7 (36.8)	10 (52.6)	14 (70.0)
Dose reduction	4 (21.1)	9 (47.4)	14 (70.0)
BGB-43395–related TEAE leading to BGB-43395 modification	7 (36.8)	10 (52.6)	16 (80.0)
Dose interruption	6 (31.6)	10 (52.6)	14 (70.0)
Dose reduction	4 (21.1)	8 (42.1)	14 (70.0)

[a]Hepatotoxicity. [b]Cholecystitis. [c]Drug-induced liver injury.
Abbreviations: BID, twice per day; TEAE, treatment-emergent adverse event.

Figure 3. Most Common (≥15% overall) TRAEs with BGB-43395 + Letrozole by Dose Arm[a] (SE2)



[a]All doses administered without food.

- TRAEs led to dose modification in 33 of 58 (56.9%) patients—the median relative dose intensities were: 240 mg, 99.6%; 400 mg, 96.8%; and 600 mg, 65.2%
- Rates of hematologic TRAEs were low and predominantly grade 1/2 across dose levels (**Table 3**)
  - There were no grade ≥3 hematologic TRAEs with BGB-43395 400 mg BID + letrozole

Table 3. Treatment-Related Hematologic Adverse Events by Dose Arm (SE2)

Hematologic adverse event, n (%)	BGB-43395 240 mg BID + letrozole (n=19) All grades	Grade ≥3	BGB-43395 400 mg BID + letrozole (n=19) All grades	Grade ≥3	BGB-43395 600 mg BID + letrozole (n=20) All grades	Grade ≥3
Neutrophil count decreased and/or Neutropenia	5 (26.3)	1 (5.3)	4 (21.1)	0	4 (20.0)	2 (10.0)
Platelet count decreased and/or Thrombocytopenia	1 (5.3)	0	0	0	1 (5.0)	0
Anemia	2 (10.5)	0	6 (31.6)	0	4 (20.0)	1 (5.0)

Abbreviation: BID, twice per day.

Effect of Administration With/Without Food on GI TRAEs

- Interim combined Cycle 1 and Cycle 2 data for patients in cohorts SE2 (n=19) and DE2 (n=20) treated with BGB-43395 400 mg BID + letrozole showed that administration with food reduced GI TRAEs (**Figure 4**)
  - Compared with those in the without food group, patients in the with food group had lower rates of GI TRAEs, all of which were grade 1
- The per-cycle rate of grades 2 and 3 diarrhea events was low and decreased with time (**Figure 5**)

Figure 4. GI TRAEs Occurring During the First 2 Cycles for BGB-43395 400 mg BID + Letrozole With vs Without Food (Combined Data From SE2 and DE2)

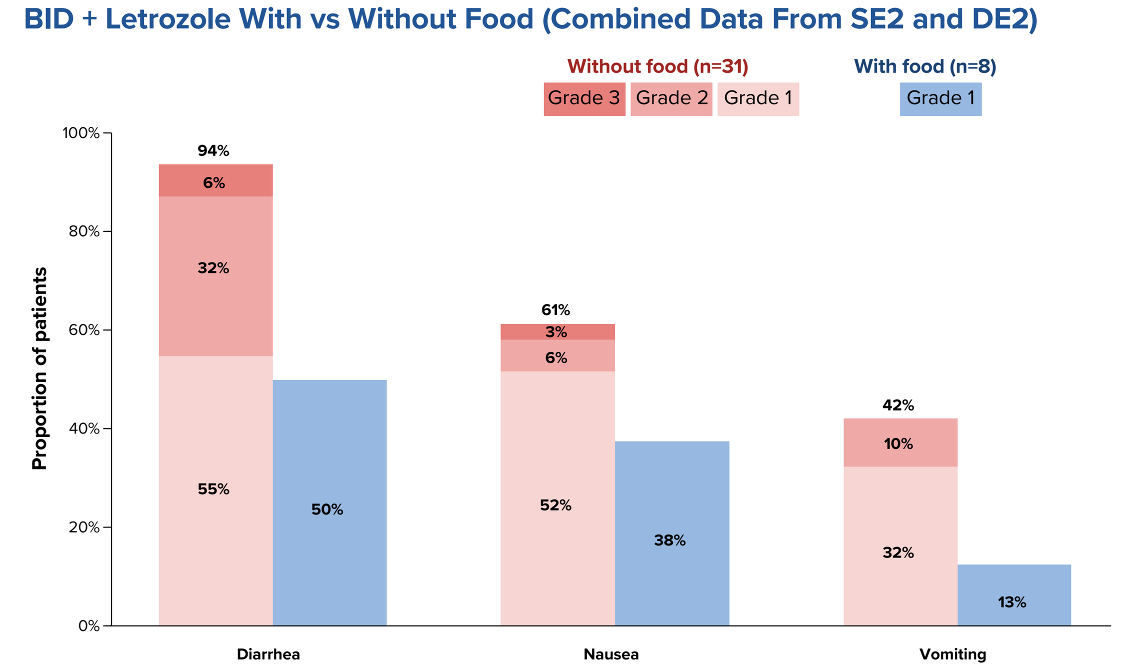
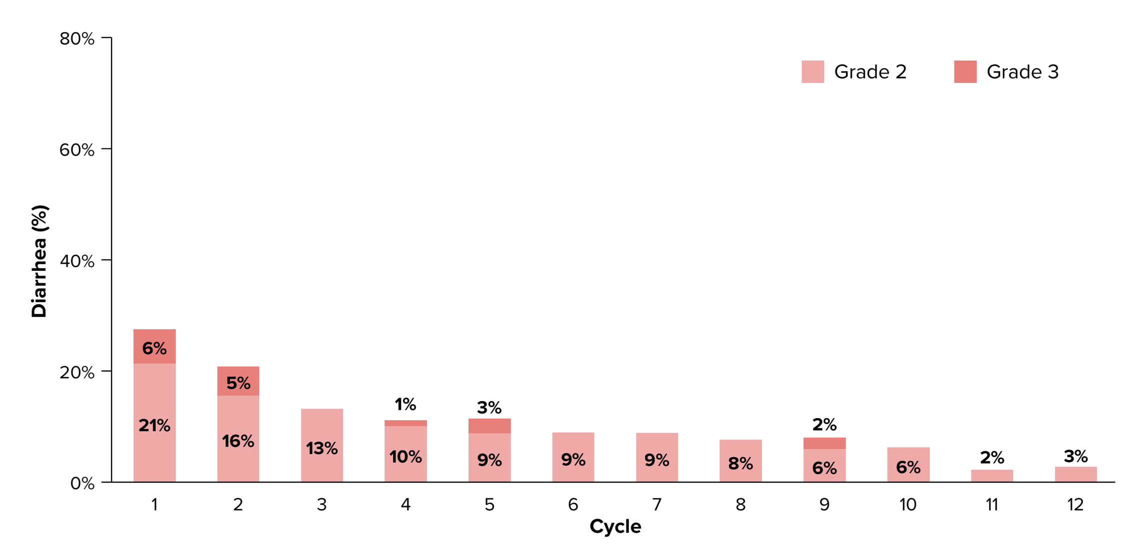


Figure 5. Prevalence of Treatment-Emergent Diarrhea (Grade ≥2), Pooled Over all Dose Levels (SE2 + DE2)[a]



[a] Maximum reported grade.

Anti-Tumor Activity

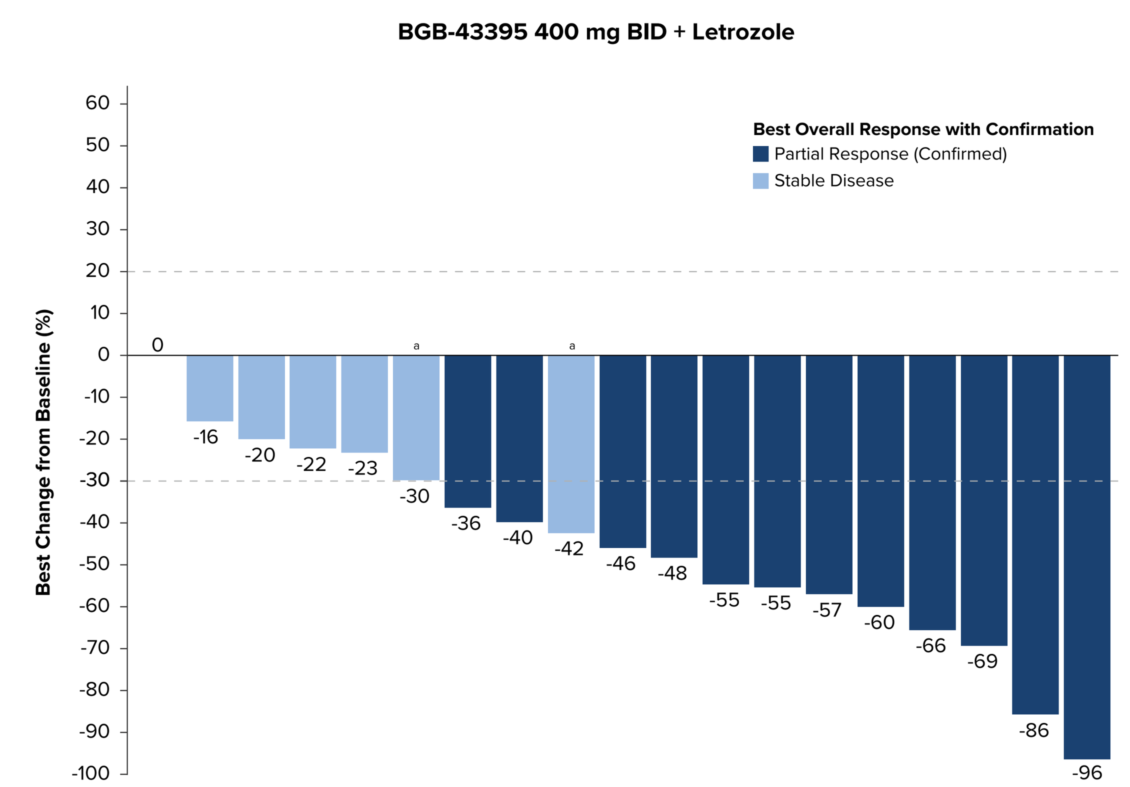
- BGB-43395 + letrozole demonstrated deep responses (**Table 4** and **Figure 6**)
  - Median time-to-response was 3.7 (range 1.6-6.0) months
  - Data for median duration of response and PFS were not yet mature; the 6-month PFS rate in the 400 mg BID arm was 94.7% (95% CI, 68.1-99.2%)
- BGB-43395 + letrozole demonstrated strong pharmacodynamic effects, indicated by TK1 reduction and ctDNA decrease

Table 4. Anti-Tumor Activity

Outcomes (responses by investigator per RECIST 1.1)	BGB-43395 240 mg BID + letrozole (n=19)	BGB-43395 400 mg BID + letrozole (n=19)	BGB-43395 600 mg BID + letrozole (n=20)
Best overall response, n (%)[a]			
Complete response	1 (5.3)	0	0
Unconfirmed partial response Confirmed partial response	13 (68.4)[b] 12 (63.2)	14 (73.7)[b] 12 (63.2)	11 (55.0) 11 (55.0)
Stable disease	5 (26.3)	7 (36.8)	8 (40.0)
Progressive disease	1 (5.3)	0	0
Not evaluable	0	0	1 (5.0)
Unconfirmed ORR (95% CI), % [n]	**73.7 (48.8-90.9) [14]**	**73.7 (48.8-90.9) [14]**	**55.0 (31.5-76.9) [11]**
Confirmed ORR (95% CI), % [n]	**68.4 (43.4-87.4) [13]**	**63.2 (38.4-83.7) [12]**	**55.0 (31.5-76.9) [11]**
Disease control rate (95% CI), %	94.7 (74.0-99.9)	100 (82.4-100)	95.0 (75.1-99.9)
Clinical benefit rate (95% CI), %[c]	94.7 (74.0-99.9)	94.7 (74.0-99.9)	75.0 (50.9-91.3)

[a]All responses confirmed unless noted.
[b]By the data cutoff date of April 30, 2026, one patient with an unconfirmed partial response remained on treatment.
[c]Best overall response of complete or partial response, or stable disease for ≥24 weeks.
Abbreviations: BID, twice per day; ORR, overall response rate.

Figure 6. Waterfall Plot Showing Best Percentage Change From Baseline (Confirmed Responses by Investigator per RECIST 1.1)



[a]Unconfirmed partial response.
Abbreviation: BID, twice per day.

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DISCLOSURES

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