First-in-human phase 1a, dose-escalation study of BGB-43395 (CDK4-selective inhibitor) as monotherapy and in combination with fulvestrant or letrozole in patients with metastatic HR+/HER2– breast cancer and other advanced solid tumors

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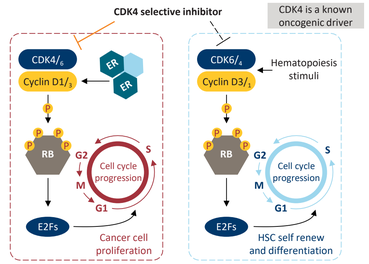
Poster No: P4-10-20
San Antonio Breast Cancer Symposium
December 10-13, 2024

Introduction

- Cyclin-dependent kinase 4 (CDK4) is a regulator of cellular transition from the G1 to the S phase of the cell cycle[1,2]
  - Although CDK4/6 inhibitors (CDK4/6i) have been approved for advanced or metastatic HR+/HER2– breast cancer (BC), patients may experience hematologic and/or gastrointestinal toxicity from these treatments, and the disease may eventually become resistant[2,3]
- BGB-43395 is a highly potent and selective orally bioavailable CDK4 inhibitor with preclinical evidence showing substantial selectivity for CDK4 over CDK6 (**Figure 1**) and antitumor activity, including in CDK4/6i-resistant BC models[4]
  - Improved selectivity may minimize hematological toxicities
  - May have activity in patients who progressed on CDK4/6i
- BGB-43395, as a single-agent or combination therapy, is being investigated in a global, open-label, dose-escalation/expansion, first-in-human study in patients with advanced or metastatic solid tumors, including HR+/HER2– BC (NCT06120283)

Figure 1. Mechanism of Action of BGB-43395



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

Objective

- To present the preliminary safety, tolerability, and PK profiles of BGB-43395 as monotherapy or with fulvestrant or letrozole from the ongoing phase 1a dose escalation study

Methods

- This phase 1 dose-escalation/expansion, open-label, multicenter trial consists of two parts (**Figure 2**)
- BGB-43395 will be administered orally QD or BID, alone or in combination with fulvestrant or letrozole

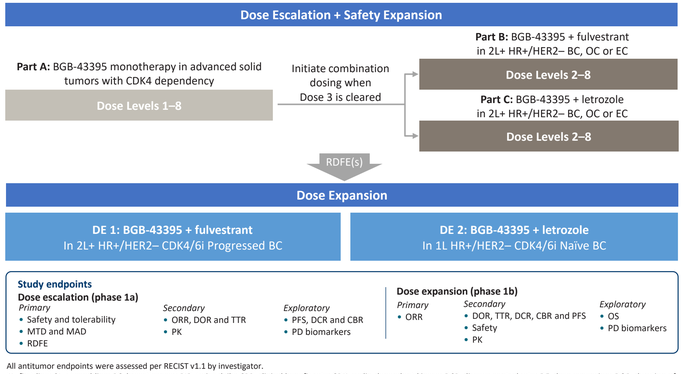
Key eligibility criteria for phase 1a

- Advanced, metastatic, or unresectable solid tumors with CDK4 dependency, including HR+/HER2- BC, HR+/HER2+ BC, prostate cancer, ovarian cancer (OC), endometrial cancer (EC), NSCLC (adenocarcinoma), gastric cancer, esophageal squamous cell carcinoma, colorectal cancer, liposarcoma, HNSCC, Ewing's sarcoma, familial melanoma, and adrenocortical carcinoma
- Part A: ≥2L of prior therapy for BC and prior standard-of-care for all other solid tumors
- Parts B and C: ≥2L of prior therapy for BC; ≥1L platinum-containing chemotherapy (CT) and ≤4 prior regimens for OC; progression following prior treatment including immune checkpoint inhibitors where appropriate for EC
- Prior CDK4i not permitted (CDK4/6i permitted where approved/available)
- Gonadotropin-releasing hormone (GnRH) agonists for ovarian function suppression (unless menopausal)
- GnRH agonists for male patients when treated with aromatase inhibitors
- ECOG PS ≤1
- Measurable disease per RECIST v1.1
- No uncontrolled/untreated brain metastases

Statistical methods

- Escalation will follow the Bayesian modified toxicity probability interval-2 design, with up to 18 patients at any dose level, including supplemental patients
- If a dose-limiting toxicity (DLT) is confirmed by the Safety Monitoring Committee at any dose level, dose escalation schema may follow modified Fibonacci sequence in consecutive dose level cohorts

Figure 2. Study Design



Study endpoints

Dose escalation (phase 1a)

Primary	*Secondary*	*Exploratory*
• Safety and tolerability • MTD and MAD • RDFE	• ORR, DOR and TTR • PK	• PFS, DCR and CBR • PD biomarkers

Dose expansion (phase 1b)

Primary	*Secondary*	*Exploratory*
• ORR	• DOR, TTR, DCR, CBR and PFS • Safety • PK	• OS • PD biomarkers

All antitumor endpoints were assessed per RECIST v1.1 by investigator.
1L, first-line; 2L, second-line; BC, breast cancer; BID, twice daily; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DCR, disease control rate; DE, dose expansion; DOR, duration of response; EC, endometrial cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MAD, maximum administered dose; MTD, maximum tolerated dose; OC, ovarian cancer; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; QD, once daily; RDFE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

Results

Study population

- As of September 23, 2024, a total of 65 patients were dosed in the ongoing dose-escalation study (see **Table 1** for baseline characteristics)
- In all, there were 13 dose levels (7 in Part A, 3 in Part B and 3 in Part C)
- All 37 HR+/HER2– BC patients in Parts A, B, and C received prior CDK4/6i, endocrine therapy, and CT, except one patient in Part B and 3 patients in Part C who did not receive CT
- Median (range) treatment follow-up was 1.8 (0.4–5.5) months for all 65 patients, 2.3 (0.4–5.5) months in Part A, 1.8 (0.5–5.1) months in Part B, and 1.8 (0.5–4.2) months in Part C

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	Part A		Part B	Part C	Total
	All (n=33)	BC* (n=6)	(n=17)	(n=15)	(N=65)
Median (range) age, years	59.0 (32.0–80.0)	53.0 (32.0–76.0)	60.0 (40.0–75.0)	54.0 (32.0–78.0)	58.0 (32.0–80.0)
Sex, n (%)					
Male	11 (33.3)	0	0	0	11 (16.9)
Female	22 (66.7)	6 (100.0)	17 (100.0)	15 (100.0)	54 (83.1)
Race, n (%)					
White	21 (63.6)	3 (50.0)	11 (64.7)	13 (86.7)	45 (69.2)
Asian	3 (9.1)	1 (16.7)	2 (11.8)	0	5 (7.7)
Tumor types, n (%)					
Breast	7 (21.2)	6 (100.0)	16 (94.1)	15 (100.0)	38 (58.5)
Colorectal	6 (18.2)	0	0	0	6 (9.2)
Liposarcoma	6 (18.2)	0	0	0	6 (9.2)
Ovarian	5 (15.2)	0	1 (5.9)	0	6 (9.2)
Other†	9 (27.3)	0	0	0	9 (13.8)
ECOG PS, n (%)					
0	13 (39.4)	4 (66.7)	6 (35.3)	8 (53.3)	27 (41.5)
1	20 (60.6)	2 (33.3)	11 (64.7)	7 (46.7)	38 (58.5)
Median (range) prior lines of therapy	4.0 (1–10)	3.5 (2–10)	5.0 (2–11)	6.0 (1–9)	5.0 (1–11)
CDK4/6i	7 (21.2)	6 (100.0)	16 (94.1)	15 (100.0)	38 (58.5)
ET	10 (30.3)	6 (100.0)	16 (94.1)	15 (100.0)	41 (63.1)
CT, including ADC	28 (84.8)	6 (100.0)	16 (94.1)	12 (80.0)	56 (86.2)
Immunotherapy	14 (42.4)	0	0	1 (6.7)	15 (23.1)
Other	21 (63.6)	4 (66.7)	8 (47.1)	10 (66.7)	39 (60.0)
Metastatic disease, n (%)	30 (90.9)	6 (100.0)	17 (100.0)	15 (100.0)	62 (95.4)
Median (range) time from initial diagnosis to first dose, years	4.8 (0.2–25.1)	9.0 (3.2–25.1)	5.4 (0.9–28.7)	9.3 (3.8–32.4)	6.3 (0.2–32.4)
Countries, n (%)					
Australia	9 (27.3)	5 (83.3)	8 (47.1)	4 (26.7)	21 (32.3)
France	5 (15.2)	0	3 (17.6)	5 (33.3)	13 (20.0)
United States	19 (57.6)	1 (16.7)	6 (35.3)	6 (40.0)	31 (47.7)

*The BC cohort for Part A includes patients with HR+/HER2- BC only. †Includes melanoma (n=1), endometrial cancer (n=3), peritoneal carcinoma (n=1), prostate cancer (n=3) and thymic carcinoma (n=1).
ADC, antibody-drug conjugate; BC, breast cancer; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ET, endocrine therapy.

Safety

- TEAEs occurred in 61/65 (93.8%) patients overall, and were primarily grades (gr) 1 and 2 (**Table 2**)
- For all 65 patients, the most common TEAEs were:
  - Diarrhea (70.8%; n=2 gr 3), nausea (44.6%; n=1 gr 3), vomiting (20.0%; n=1 gr 3), fatigue (16.9%; n=1 gr 3), neutrophil count decreased (16.9%, n=2 gr 3)
- Low rates of treatment-emergent hematological toxicities for all 65 patients, with most events being gr 1 and 2*:
  - Neutrophil count decreased (16.9%, n=2 gr 3)/neutropenia (4.6%, n=2 gr 3, n=1 gr 4), anemia (12.3%, n=3 gr 3), platelet count decreased (6.2%, n=2 gr 3) /thrombocytopenia (3.1%, n=2 gr 3), WBC decreased (6.2%, n=1 gr 3)
- Treatment-related TEAEs were primarily gr 1 and 2; most common events are shown in **Table 3**
- Serious adverse events (SAEs) occurred in 9.2% of patients overall (**Table 2**)
- There were no DLTs

*One uncoded grade 2 event, 'Uncoded: decreased neutrophil', was excluded from the summary count.

Table 2. Safety Summary

Event type, n (%)	Part A		Part B	Part C	Total
	All (n=33)	BC (n=6)	(n=17)	(n=15)	(N=65)
Any TEAE	33 (100.0)	6 (100.0)	15 (88.2)	13 (86.7)	61 (93.8)
Grade ≥3 TEAEs	10 (30.3)	2 (33.3)	4 (23.5)	1 (6.7)	15 (23.1)
Treatment-related TEAE	31 (93.9)	6 (100.0)	14 (82.4)	12 (80.0)	57 (87.7)
Grade ≥3 treatment-related TEAEs	9 (27.3)	1 (16.7)	1 (5.9)	0	10 (15.4)
Any TESAEs	3 (9.1)	1 (16.7)	2 (11.8)	1 (6.7)	6 (9.2)
Fatal TESAEs	1 (3.0)*	0	0	0	1 (1.5)
Leading to study treatment discontinuation	2 (6.1)	1 (16.7)	0	1 (6.7)	3 (4.6)

AEs per NCI-CTCAE v5.0 by type, frequency, severity, timing, seriousness and relationship to drug.
*One patient had treatment-emergent sepsis (not treatment-related) which led to death. AE, adverse event; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Table 3. Most Common Treatment-Related TEAEs in >10% of Patients

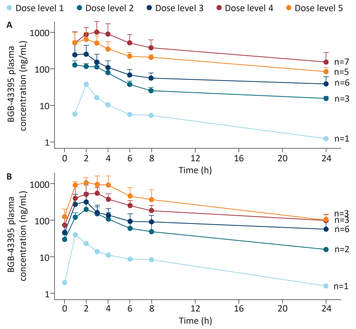
Event type, n (%)	Part A		Part B	Part C	Total
	All (n=33)	BC (n=6)	(n=17)	(n=15)	(N=65)
Diarrhea	24 (72.7)	2 (33.3)	9 (52.9)	9 (60.0)	42 (64.6)
Grade ≥3	2 (6.1)	0	0	0	2 (3.1)
Nausea	18 (54.5)	3 (50.0)	4 (23.5)	5 (33.3)	27 (41.5)
Grade ≥3	1 (3.0)	0	0	0	1 (1.5)
Vomiting	9 (27.3)	0	2 (11.8)	1 (6.7)	12 (18.5)
Grade ≥3	1 (3.0)	0	0	0	1 (1.5)
Neutrophil count decreased	4 (12.1)	1 (16.7)	5 (29.4)	1 (6.7)	10 (15.4)
Grade ≥3	2 (6.1)	0	0	0	2 (3.1)
Decreased appetite	6 (18.2)	0	1 (5.9)	1 (6.7)	8 (12.3)
Grade ≥3	0	0	0	0	0
Fatigue	4 (12.1)	2 (33.3)	2 (11.8)	2 (13.3)	8 (12.3)
Grade ≥3	0	0	0	0	0

Results

Pharmacokinetics

- BGB-43395 was rapidly absorbed after oral administration with median T_{max} occurring ~after 2 hours; limited accumulation was observed with repeated dosing (**Figure 3**)
- BGB-43395 exposures increased approximately dose proportionately in the available dose range

Figure 3. (A) Single Dose and (B) Repeated Dose Pharmacokinetics of BGB-43395 in Monotherapy



Only the PK data of patients who received once daily dosing in Part A are shown; PK data have fewer dose levels than the study schema because not all dose levels have been explored yet.

Conclusions

- BGB-43395 is a novel, potential best-in-class, CDK4 inhibitor with high potency and selectivity for tumors with high CDK4 dependency, with the potential to minimize off-target toxicity
- The totality of data supports the continued development of BGB-43395
  - Across different dose levels, BGB-43395 has been generally safe and tolerable, as monotherapy and in combination with endocrine therapy, with low rates of hematologic toxicities
  - BGB-43395 has exhibited rapid absorption and linear PK in the linear dose range
- As the study advances, encouraging PD data, as well as preliminary clinical activity, are emerging; study data updates will be reported at a future medical conference

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Acknowledgments

We would like to thank the investigators, site support staff, and especially the patients for participating in this study. This study is sponsored by BeiGene. Medical writing support was provided by AMICULUM USA, with funding provided by BeiGene.