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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ABSTRACT

Background: Despite the approval of cyclin-dependent kinase (CDK) 4/6 inhibitors (CDK4/6i) in HR+/HER2− breast cancer (BC), pts may develop resistance and experience toxicities with current treatments. BGB-43395 is a potent and selective CDK4i, showing preclinical antitumor activity with improved CDK4 coverage and greater selectivity for CDK4 over CDK6, thus minimizing off-target toxicity and potentially toxicity-related dose reduction/discontinuations. Here, we present the preliminary results of an ongoing first-in-human, phase 1a dose escalation, open-label, multicenter trial of BGB-43395 given orally as monotherapy in pts with advanced solid tumors (Part A) or as part of combination therapy in pts with fulvestrant (Part B) or letrozole (Part C) in pts with 2L+ HR+/HER2− BC (NCT06120283).

Methods: Eligible pts were ≥18 years of age with histologically or cytologically confirmed advanced, metastatic, or unresectable solid tumors associated with CDK4 dependency. Permitted prior therapies included ≥2 lines of treatment including endocrine therapy (ET) and CDK4/6i in either the adjuvant or advanced metastatic setting for pts with HR+/HER2− BC, ≥2 lines of HER2 targeted therapy for pts with HR+/HER2+ BC, and standard of care for pts with other advanced solid tumors. Primary objectives were to assess the safety and tolerability of BGB-43395 as monotherapy or combined with fulvestrant or letrozole, and to determine the maximum tolerated dose or maximum administered dose and the recommended dose for expansion. Secondary endpoints were to evaluate pharmacokinetics and preliminary antitumor activity assessed per RECIST v1.1 by investigator.

Results: As of May 20, 2024, 23 pts (17 in Part A [including 6 with HR+/HER2− BC], 3 in Part B, and 3 in Part C) were enrolled in the ongoing dose escalation portion of the study. In all, there were 7 dose cohorts (5 in Part A, 1 in Part B and 1 in Part C). In Parts A, B and C, respectively, 14/17 (82.4%), 2/3 (66.7%) and 3/3 (100%) pts had metastatic disease. The median (range) number of lines of prior therapy was 3.0 (1–10) in all pts in Part A (3.5 [2–10] in the 6 HR+/HER2− pts in Part A), 4.0 (2–8) in Part B, and 4.0 (1–5) in Part C. All of the 12 HR+/HER2− BC pts in Parts A, B, and C, received prior CDK4/6i, ET, and chemotherapy (CT), except 1 pt in Part C who did not receive CT. TEAEs occurred in 15/17 (88.2%), 1/3 (33.3%) and 0 pts in Parts A, B, and C, respectively, and were primarily grades 1 and 2. For all 23 patients, the most common TEAEs were diarrhea (12/23; 52.2%; 1 pt grade 3), nausea (7/23; 30.4%; all grades 1 and 2), anemia (3/23; 13.0%; 1 pt grade 3), fatigue (3/23; 13.0%; all grades 1 and 2), and vomiting (3/23; 13.0%; all grades 1 and 2). Treatment-related AEs occurred in 14/23 (60.9%) pts (13 in Part A, 1 in Part B and 0 in Part C) and were primarily grade 1 and 2 except

for 3 pts with grade 3. There were no DLTs or TEAEs leading to treatment discontinuation or death. Updated clinical data will be presented.

Conclusion: BGB-43395 is a novel CDK4-selective inhibitor and a promising agent for tumors with high CDK4 dependency with the potential to minimize off-target toxicity. To date, BGB-43395 has been safe and tolerable, supporting continued development**.** The dose-escalation phase is currently ongoing.