Trial in progress: First-in-human phase 1a/1b, dose-escalation/expansion study of BGB-43395 (CDK4 selective inhibitor) as monotherapy or combination therapy in Chinese patients with metastatic HR+/HER2− breast cancer and other advanced solid tumors

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ABSTRACT

Background: Dysregulation of cyclin-dependent kinase (CDK) 4 is observed in various solid tumors. CDK4/6 inhibitors provide substantial clinical benefit; however, pts with advanced or metastatic HR+/HER2− breast cancer (BC) eventually develop resistance and may experience toxicities associated with current treatments. BGB-43395 is a potent, selective, orally bioavailable CDK4 inhibitor, with preclinical evidence showing antitumor activity and substantial selectivity for CDK4 over CDK6, thus minimizing off-target toxicity and potentially toxicity-related dose reduction/discontinuations, and therefore supporting further evaluation in pts.

Methods: This phase 1a/1b, open-label, multicenter study is evaluating the safety, tolerability, PK, pharmacodynamics (PD), and preliminary antitumor activity of BGB-43395 given orally as monotherapy or in combination with fulvestrant, letrozole, or other combination partners in Chinese pts with advanced or metastatic solid tumors, including HR+/HER2− BC (NCT06253195). In the dose-escalation phase (phase 1a), sequential cohorts of pts with advanced solid tumors will receive increasing dose levels of BGB-43395 given orally as monotherapy (Part A) and cohorts of pts with 2L+ HR+/HER2− BC will receive increasing dose levels of BGB-43395 in combination with either fulvestrant (Part B) or letrozole (Part C). In the dose-expansion phase (phase 1b), pts with advanced or metastatic HR+/HER2− BC will receive the recommended dose for expansion (RDFE) of BGB-43395 in combination with fulvestrant. Eligible pts are ≥18 years of age with histologically or cytologically confirmed locally advanced or metastatic solid tumors associated with CDK4 dependency who have received prior standard-of-care therapy, including ≥1 line of treatment for locally advanced or metastatic disease and prior endocrine therapy and a CDK4/6 inhibitor in either the adjuvant or locally advanced or metastatic setting for HR+/HER2− BC, or ≥2 lines of HER2-targeted therapy for pts with HR+/HER2+ BC (phase 1a); locally advanced or metastatic HR+/HER2− BC in pts who have received ≥1 line of treatment for locally advanced or metastatic disease and prior endocrine therapy and a CDK4/6 inhibitor (phase 1b); and ECOG PS ≤1. For phase 1a, the primary objectives are to assess the safety and tolerability of BGB-43395 monotherapy or as part of combination therapy, and to determine the maximum tolerated dose, maximum administered dose and RDFE; secondary objectives are to assess preliminary antitumor activity (ORR, duration of response [DoR] and time to response [TTR] as assessed by the investigator per RECIST v1.1) and the PK of BGB-43395. Exploratory endpoints are PFS as assessed per investigator, disease control rate (DCR) and clinical benefit rate (CBR) per RECIST v1.1, PD, and assessment of biomarkers associated with response. For phase 1b, the primary objective is to assess the antitumor activity of BGB-43395 (ORR assessed by the investigator); secondary objectives are to further assess the antitumor activity (DoR, TTR, DCR, CBR, and PFS assessed by the investigator), safety and tolerability, and PK of BGB-43395. Exploratory endpoints are overall survival and potential biomarkers associated with response. As of May 28,

2024, the study is currently enrolling pts, with five pts currently dosed in the dose-escalation phase across 12 sites in China.