Trial in progress: A first-in-human phase 1a/b, dose-escalation/expansion study of BG-68501/ETX-197 (CDK2 inhibitor) as monotherapy or in combination with fulvestrant for patients with HR+/HER2− breast cancer and other advanced solid tumors

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ABSTRACT

Background: Cyclin-dependent kinase (CDK) 2 can regulate the cell cycle through the interaction with cyclin E or cyclin A during the G1/S and S/G2 transitions, respectively. Elevated CDK2 activity is a key resistance mechanism to CDK4/6 inhibition in HR+/HER2− breast cancer (BC). Other genomic alterations, eg, loss of RB1, can cause resistance in additional solid tumors, including high-grade serous ovarian cancer, gastric cancer, small cell lung cancer (SCLC), and endometrial cancers. *CCNE1* amplification or cyclin E overexpression may confer sensitivity to CDK2 inhibition. BG-68501/ETX-197 is a potent, selective inhibitor of CDK2, with preclinical evidence showing potent activity in biochemical and cellular assays, marked antitumor activity in cancer xenograft models, and superior selectivity for CDK2 over other CDK family members.

Methods: This study is a first-in-human, phase 1a/b, open-label, multicenter study to evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary antitumor activity of BG-68501/ETX-197 in pts with advanced, nonresectable, or metastatic solid tumors, including HR+/HER2− BC. In the dose-escalation phase (phase 1a), sequential cohorts will receive increasing doses of BG-68501/ETX-197 as monotherapy, or in combination with fulvestrant; additionally, safety expansion cohorts will receive BG-68501/ETX-197 at doses recommended for further evaluation. In the dose-expansion phase (phase 1b), pts with HR+/HER2− BC, platinum-refractory or -resistant serous ovarian, fallopian tube, primary peritoneal cancer (PROC), extensive-stage SCLC (ES-SCLC), or *CCNE1*-amplified advanced solid tumors will receive BG-68501/ETX-197 orally as monotherapy or combined with fulvestrant. Eligibility criteria include pts ≥18 years with histologically or cytologically confirmed advanced or metastatic solid tumors potentially associated with CDK2 dependency who have received ≥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 prior standard of care for all other advanced solid tumors. For the dose-escalation phase (phase 1a), the primary objectives are to assess the safety and tolerability of BG-68501/ETX-197 monotherapy or in combination with fulvestrant, and to determine the maximum tolerated dose, maximum administered dose, and recommended dose for expansion (RDFE); secondary objectives are to assess preliminary antitumor activity (ORR, duration of response [DoR], time to response [TTR], disease control rate [DCR] and clinical benefit rate [CBR]) as assessed by investigator per RECIST v1.1, and PK. For the dose-expansion phase (phase 1b), the primary objectives are to assess the antitumor activity (ORR) of BG-68501/ETX-197 in combination with fulvestrant in pts with HR+/HER2− advanced or metastatic BC, and BG-68501/ETX-197 as monotherapy in pts with PROC, ES-SCLC, and other advanced or metastatic solid tumors with *CCNE1* amplification; secondary objectives are to further assess the antitumor activity (DoR, TTR, DCR and CBR) of BG-68501/ETX-197 alone in the previously mentioned advanced solid tumors or in combination with fulvestrant in

HR+/HER2− metastatic BC, and to assess the safety and tolerability and PK of BG-68501/ETX-197 at the RDFE (NCT06257264). The study is currently recruiting pts, with 14 sites open across two countries and 6 pts enrolled. Enrollment is complete for 1 cohort and cohort 2A is currently enrolling pts.