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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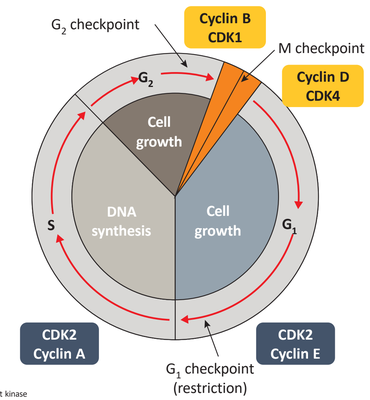
Introduction

- CDKs are important regulators of cell cycle progression (**Figure 1**)
- Inhibition of CDKs has been shown to have antiproliferative effects on tumor cells[1]
- Targeting both CDK2 and CDK4/6 may lead to improved antitumor activity[2,3]
- BG-68501/ETX-197 is a potent inhibitor of CDK2 with preclinical evidence showing strong antitumor activity and superior selectivity for CDK2 over other CDK family members[4]
- This is a first-in-human, phase 1a/b, open-label, multicenter trial to evaluate the safety, tolerability, PK, and preliminary antitumor activity of oral BG-68501/ETX-197
- BG-68501/ETX-197 will be given as monotherapy for patients with advanced, nonresectable, or metastatic solid tumors, and in combination with fulvestrant ± BGB-43395 (a highly potent, selective, and orally available CDK4 inhibitor[3]) for patients with HR+/HER2− breast cancer (BC) (NCT06257264)

Figure 1. CDK2 Forms a Complex with Cyclin E and Cyclin A to Regulate the G_1/S and S/G_2 Cell Cycle Transitions



CDK, cyclin-dependent kinase

Methods

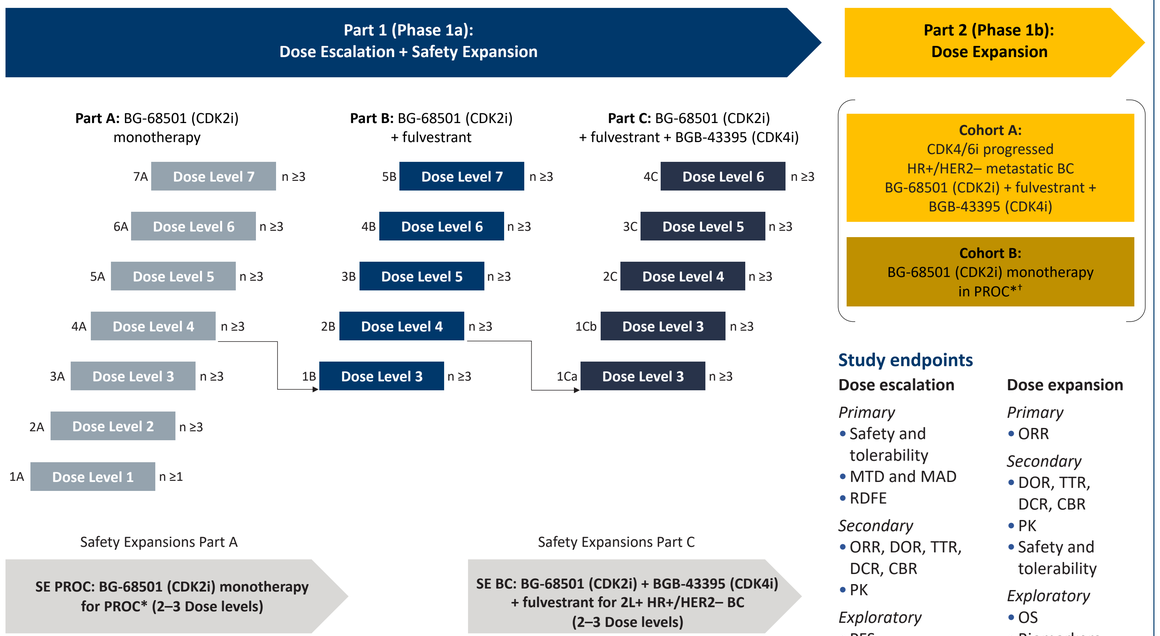
Study design

- This is a phase 1, open-label, multicenter trial consisting of two parts: dose escalation and expansion (**Figure 2**)

Figure 2. Study Design

Key eligibility criteria

- ≥18 years
- Advanced or metastatic solid tumors potentially associated with CDK2 dependency
- Prior available SOC systemic therapies
  - For HR+/HER2– BC: ≥1L for advanced or metastatic disease, including prior ET and a CDK4/6i (where approved/available) in either the adjuvant or advanced/metastatic setting
  - For PROC: ≥1L of platinum-containing CT for advanced disease; ≤4L in the advanced/metastatic setting
- GnRH agonists for ovarian function suppression (unless menopausal)
- GnRH agonists for males treated with fulvestrant
- ECOG PS ≤1
- Measurable disease per RECIST v1.1
- No uncontrolled/untreated brain metastases
- No prior therapy selectively targeting CDK2



Study endpoints

Dose escalation

Primary
- Safety and tolerability
- MTD and MAD
- RDFE

Secondary
- ORR, DOR, TTR, DCR, CBR
- PK

Exploratory
- PFS
- Biomarkers

Dose expansion

Primary
- ORR

Secondary
- DOR, TTR, DCR, CBR
- PK
- Safety and tolerability

Exploratory
- OS
- Biomarkers

Inclusion criteria for the Safety Expansion Parts A and C matches inclusion criteria for the equivalent Phase 1b dose expansion cohorts.
*Including fallopian tube or primary peritoneal cancer. †Patients may be selected based on cyclin E1 expression; cut-off to be determined.
2L+, second-line or greater; CBR, clinical benefit rate; DCR, disease control rate; DOR, duration of response; ET, endocrine therapy; MAD, maximum administered dose; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PROC, platinum-refractory or resistant serous ovarian cancer; RDFE, recommended dose for expansion; RECIST, response evaluation criteria in solid tumors; SE, safety expansion; TTR, time to response.

Methods

Statistical methods

- The dose escalation will proceed according to the modified toxicity probability interval-2 method[5,6]
- Data collected will be reported using summary tables and figures. Categorical variables will be summarized by frequency distributions, and continuous variables will be summarized by descriptive statistics
- For time-to-event variables, percentages of patients experiencing that event will be presented, and median time-to-event will be estimated using Kaplan–Meier methodology

Conclusions

- BG-68501/ETX-197 is being assessed as monotherapy for patients with advanced solid tumors and in combination with fulvestrant ± BGB-43395 for patients with HR+/HER2− BC in a first-in-human, phase 1, dose-escalation and expansion study
- This study will provide insights into the clinical effects of targeting CDK2 in solid tumors
- As of October 29, 2024, recruitment is ongoing, with 11 sites open across 3 countries (Australia, China, and US) and 21 patients dosed

Contact

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