# 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

Jian Zhang,[1] Zhanmin Zhang,[2] Yuping Sun,[3] Tao Qin,[4] Ping Zhou,[5] Gilbert Y. Wong,[6] Yiran He,[7] Zhimin Shao[1]

[1]Fudan University Shanghai Cancer Center, Shanghai, China; [2]The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China; [3]Shandong Cancer Hospital, Jinan, Shandong, China; [4]Sun Yat-sen Memorial Hospital, Sun Yat-sen University (South Campus), Guangzhou, Guangdong, China; [5]Clinical Development Solid Tumors, BeiGene (Shanghai) Co., Ltd., Shanghai, China; [6]BeiGene USA, Inc, San Mateo, CA, USA; [7]Statistics for Early Development, BeiGene (Beijing) Co., Ltd., Beijing, China

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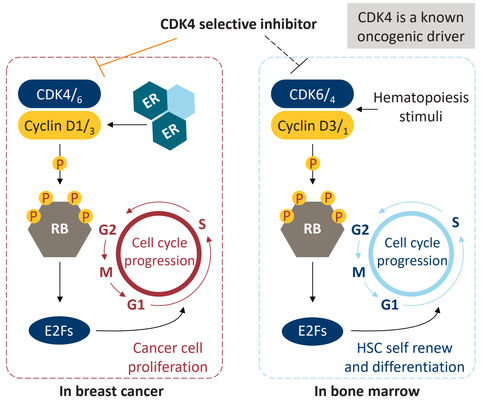
## Introduction

- Cyclin-dependent kinase 4 (CDK4) is a regulator of cellular transition from the G1 to the S phase of the cell cycle[1,2]
- Dysregulation of the cyclin D-CDK4-Rb pathway has been reported in various types of solid tumors[1]
- Despite the approval of CDK4/6 inhibitors (CDK4/6i) for patients with advanced or metastatic HR+/ HER2− breast cancer (BC), advanced disease becomes resistant, and patients may experience hematologic and/or gastrointestinal toxicity[2,3]
- BGB-43395 is a highly potent and selective orally bioavailable CDK4i (**Figure 1**), with preclinical evidence showing substantial selectivity for CDK4 over CDK6 and antitumor activity[4]
  - Improved selectivity may minimize hematological toxicities
- BGB-43395, as a single-agent or combination therapy, is being investigated in an open-label, dose-escalation/expansion, first-in-human study in Chinese patients with advanced or metastatic solid tumors, including HR+/HER2− BC (NCT06253195)

### 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

## Methods

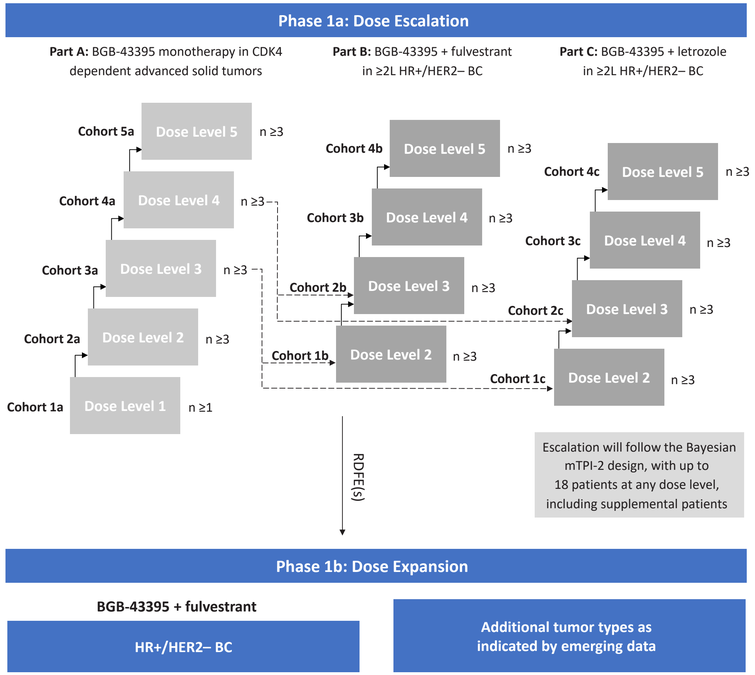
### Study design

- 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 either fulvestrant or letrozole

### Figure 2. Study Design

#### Key eligibility criteria

- Advanced or metastatic solid tumors with CDK4 dependency
- Phase 1a:
  - Prior SOC required for all tumor types (if available and tolerated)
  - HR+/HER2− BC: ≥1L of prior therapy, including ET and CDK4/6i
  - HR+/HER2+ BC: ≥2 prior HER2-targeted therapies
- Phase 1b:
  - ≥1L of prior therapy for HR+/HER2− BC, including ET and CDK4/6i
  - ≤2L of prior cytotoxic CT allowed
- Prior CDK4i not permitted
- GnRH agonists for ovarian function or gonadal suppression in pre-/peri-menopausal females or males, respectively, with HR+/HER2− BC
- ECOG PS ≤1
- Measurable disease per RECIST v1.1
- No uncontrolled/untreated brain metastases




#### Study endpoints

**Dose escalation (phase 1a)**

*Primary*
- Safety and tolerability
- MTD and MAD
- RDFE

*Secondary*
- ORR, DOR and TTR
- PK

*Exploratory*
- PFS, DCR and CBR
- Biomarkers

**Dose expansion (phase 1b)**

*Primary*
- ORR

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

*Exploratory*
- OS
- Biomarkers

Tumor response will be assessed by the investigator per RECIST v1.1

1L, first line; 2L, second line; BID, twice daily; CBR, clinical benefit rate; CT, chemotherapy; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ET, endocrine therapy; GnRH, gonadotropin-releasing hormone; HER2, human epidermal growth factor 2; HR, hormone receptor; MAD, maximum administered dose; MTD, maximum tolerated dose; mTPI-2, modified toxicity probability interval-2; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; QD, once daily; RDFE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumors; SOC, standard of care; TTR, time to response.

## Methods

### Statistical methods

- If a dose-limiting toxicity is confirmed by the Safety Monitoring Committee at any dose level, dose escalation schema may follow modified Fibonacci sequence in consecutive dose level cohorts[5]
- ORR, DCR and CBR will be summarized by dose level within each therapy in dose escalation and by dose level within each tumor type in dose expansion, along with 95% CI. PFS, DOR, TTR and OS will be summarized by dose level within each tumor type in the dose-expansion phase and estimated using Kaplan-Meier methodology
  - No formal hypothesis testing will be performed in the antitumor activity evaluation

## Conclusions

- BGB-43395 is a novel, potential best-in-class, highly potent and selective CDK4 inhibitor with the potential to minimize off-target toxicity
- BGB-43395 is being evaluated as monotherapy in Chinese patients with CDK4-dependent advanced solid tumors, and combined with fulvestrant or letrozole in HR+/HER2− BC in a first-in-human, phase 1, dose-escalation/expansion study
- This study will provide insights into the clinical effect of targeting CDK4 in solid tumors, including HR+/HER2− BC
- As of September 24, 2024, the study is currently enrolling patients, with 21 patients currently dosed in the dose-escalation phase across 12 sites in China
- For a list of participating sites, please refer to ClinicalTrials.gov, NCT06253195

## Contact

Prof Jian Zhang
Fudan University Shanghai Cancer Center, Shanghai, China
syner2000@163.com

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