Trial In Progress: A Phase 1 Dose-Escalation Study Evaluating BGB-21447 (BCL2 Inhibitor) In Combination With Fulvestrant With And Without BGB-43395 (CDK4 Inhibitor) In Patients With Previously Treated HR+/HER2− Metastatic Breast Cancer

PS5-07-29

Geoffrey J. Lindeman,[1] Christine Muttiah,[2] Peter Lau,[3] Natasha Hunter,[4] Jian Zhang,[5] Yang Liu,[6] Yan Dong,[7] Ping Zhou,[6] Ami Kavi,[7] Kiana Keyvanjah,[7] Zhimin Shao[5]

[1]Peter MacCallum Cancer Centre, and The Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia; [2]Western Health, Melbourne, VIC, Australia; [3]Linear Clinical Research, Nedlands, WA, Australia; [4]Fred Hutchinson Cancer Center, Seattle, WA, USA; [5]Fudan University Shanghai Cancer Center, Shanghai, China; [6]BeOne Medicines (Shanghai) Co., Ltd, Shanghai, China; [7]BeOne Medicines Ltd, San Carlos, CA, USA

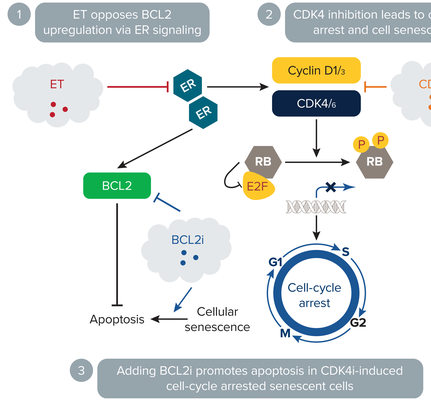
CONCLUSIONS

- BGB-21447 is a novel, highly potent and selective BCL2i, with the potential to improve antitumor activity when combined with fulvestrant and BGB-43395 compared with singlet or doublet therapy in patients with HR+/HER2− metastatic breast cancer
- BGB-21447 plus fulvestrant with or without BGB-43395 is being evaluated in HR+/HER2− metastatic breast cancer in this phase 1 clinical trial
- This trial will provide insights into the clinical effect of targeting BCL2 and CDK4 in patients with previously treated HR+/HER2− metastatic breast cancer
- As of October 27, 2025, the trial is currently enrolling patients at 15 sites in 3 countries (**Figure 4**)
- For a list of participating sites, please refer to ClinicalTrials.gov, NCT06756932

INTRODUCTION

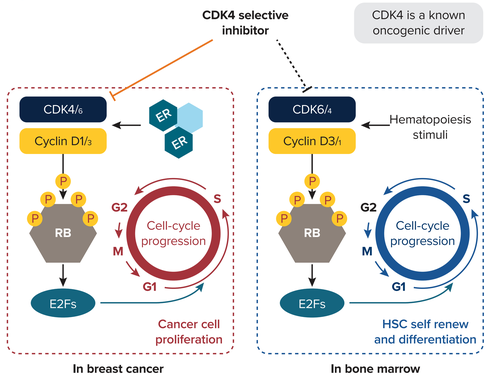
- Hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) tumors account for approximately 70% of all breast cancers and are responsible for most breast cancer-related deaths[1,2]
  - Cyclin dependent kinase 4/6 inhibitors (CDK4/6i) combined with endocrine therapy (ET) have significantly improved outcomes compared with ET alone for the treatment of HR+/HER2− advanced breast cancer;[3] however, most patients eventually experience disease progression, highlighting an unmet need for new therapies
- B-cell lymphoma 2 (BCL2) is an anti-apoptotic protein involved in regulation of the intrinsic apoptosis pathway that is often dysregulated in tumors
  - In breast cancer, estrogen receptor (ER) signaling leads to upregulation of BCL2, which is estimated to be overexpressed in approximately 70-80% of HR+ breast cancer[2,4,5]
  - BCL2 inhibitors (BCL2i) in rational combinations with other anticancer agents may enhance potential antitumor effects[2]
  - Preclinical experiments with HR+ breast cancer mouse xenograft models showed the addition of a BCL2i to ET enhanced antitumor activity relative to single-agent ET[6]
  - Furthermore, the addition of a CDK4i or CDK4/6i to a BCL2i + ET augmented this antitumor activity in preclinical and clinical studies, suggesting further exploration of the triplet is warranted[7-9]
- BGB-21447 is a novel, orally bioavailable, next-generation BH3 mimetic designed to be a highly potent inhibitor of both wild-type and mutant BCL2, also active against BCL-xL (**Figure 1**)
  - BGB-21447 is currently in clinical trials for hematologic cancers and breast cancer (NCT05828589, NCT06756932)
- BGB-43395 is a selective CDK4i with improved CDK4 coverage and greater selectivity for CDK4 over CDK6, thus achieving more potent CDK4 inhibition, while minimizing off-target toxicities (**Figure 2**)
  - BGB-43395 is currently under development with ET in HR+ breast cancer and other selected solid tumors (NCT06120283, NCT06253195)
- Here, we describe an ongoing phase 1 study of BGB-21447 plus fulvestrant with or without BGB-43395 (NCT06756932)

Figure 1. Mechanism of Action of BGB-21447, BGB-43395, and ET



Abbreviations: P, phosphate; RB, retinoblastoma protein.

Figure 2. Mechanism of Action of BGB-43395



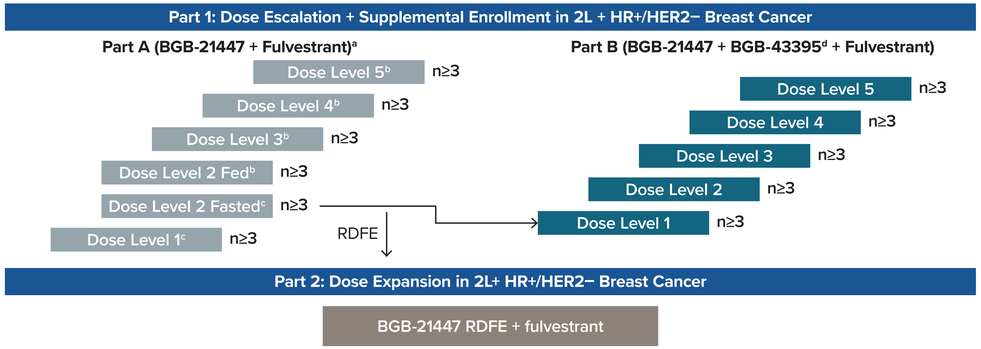
Abbreviation: HSC, hematopoietic stem cell.

METHODS

Trial Design

- This phase 1, open-label, international, multicenter dose-escalation and -expansion trial consists of two parts (**Figure 3**)
  - BGB-21447 will be administered orally with fulvestrant in Part 1A, and with fulvestrant and BGB-43395 in Part 1B
  - BGB-21447 recommended dose for expansion (RDFE) will be administered orally at 1-3 dose levels with fulvestrant in Part 2

Figure 3. Study Design



Key Eligibility Criteria

- ≥18 years (or the legal age of consent in the jurisdiction in which the study is taking place)
- Histologically/cytologically confirmed 2L+ HR+/HER2− metastatic breast cancer
- Parts 1A and 1B: ≥1 prior line(s) of treatment for advanced/metastatic disease, including prior ET and CDK4/6i
  - Part 2: 1-3 lines of prior treatment for advanced/metastatic disease, including prior ET and CDK4/6i in either the adjuvant or advanced/metastatic setting
  - Prior targeted therapies (if available and tolerated) for known actionable genomic alterations
- ECOG PS ≤1
- GnRH agonists for ovarian function suppression (or be post-menopausal)
- GnRH agonists for male patients when treated with fulvestrant at the discretion of the investigator
- For supplemental enrollment in dose escalation and enrollment to dose expansion, central confirmation of BCL2 immunohistochemistry 2+/3+
- For dose escalation, measurable disease per RECIST v1.1, and bone only disease without measurable disease. For supplemental enrollment and dose expansion, ≥1 measurable lesion per RECIST v1.1
- Prior BCL2i exposure not permitted. Prior therapy selectively targeting CDK4 not permitted (for triplet combination cohorts only)
- No uncontrolled/untreated brain metastases

Endpoints

Dose escalation – Part 1 A/B

- Primary
  - Safety/tolerability
  - MTD/MAD, RDFE
- Secondary
  - ORR, DOR, TTR
  - PK
  - Effect of food on PK (food effect substudy)

Dose expansion – Part 2

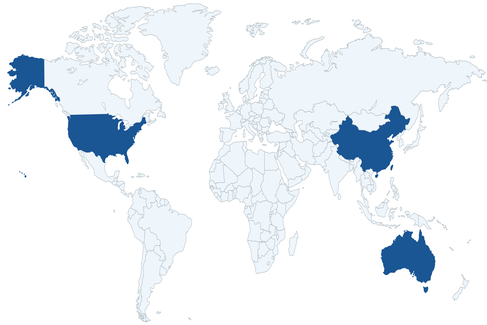
- Primary
  - ORR
- Secondary
  - DOR, DCR, CBR, PFS
  - Safety/tolerability
  - PK

All response endpoints will be assessed per investigator by RECIST v1.1.
Alternative dosing schedules (eg, twice daily or 3 weeks of treatment with 1 week off treatment per cycle) may be evaluated based on emerging data and in consultation with the SMC. A food effect substudy may be enrolled separately from dose escalations shown here to evaluate the effect of food on the PK of BGB-21447 in approximately 12-15 patients.
[a]Supplemental enrollment for dose-escalation cohorts of patients centrally confirmed for BCL2 IHC 2+ and 3+. [b]A cohort of DL 2 will be administered with a light meal and will enroll approximately 3-12 patients. If patients do not complete necessary assessments or the data are incomplete for reasons other than DLT, patients may be replaced in this cohort. All cohorts enrolling after DL 2 Fed will be administered BGB-21447 with a light meal. Based on emerging data and upon consultation with SMC, administration of BGB-21447 may change with respect to food. [c]Doublet dose-escalation DL 1 and 2 will be administered under fasted conditions. [d]BGB-43395 will be administered at its RDFE.
Abbreviations: 2L, second-line; CBR, clinical benefit rate; DCR, disease control rate; DL, dose level; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GnRH, gonadotrophin-releasing hormone; MAD, maximum administered dose; MTD, maximum tolerated dose; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; SMC, Safety Monitoring Committee; TTR, time to response.

Analysis and Statistical Methods

- The dose escalation will proceed according to the modified toxicity probability interval-2 method[10]
- Safety and antitumor activity endpoints will be summarized by dose level cohorts

Figure 4. Participating Countries



REFERENCES

1. Burstein HJ. *N Engl J Med*. 2020;383:2557-2570.
2. Lok SW, et al. *Cancer Discov*. 2019;9:354-369.
3. Thill M, Schmidt M. *Ther Adv Med Oncol*. 2018;3:1758835918793326.
4. Kawiak A, Kostecka A. *Cancers (Basel)*. 2022;14:279.
5. Dawson SJ, et al. *Br J Cancer*. 2010;103 :668-675.
6. Vaillant F, et al. *Cancer Cell*. 2013;24:120-129.
7. Whittle JR, et al. *Clin Cancer Res*. 2020;26:4120-4134.
8. Lindeman G, et al. *Clin Cancer Res*. 2025;31(12_Suppl):P2-07-18.
9. BeOne Medicines, unpublished data.
10. Guo W, et al. *Contemp Clin Trials*. 2017;58:23-33.

DISCLOSURES

GJL reports consulting or advisory fees from Pfizer; research funding from AbbVie, Amgen, Genentech/Roche, and Pfizer; and patents, royalties, or other intellectual property from AbbVie and Genentech.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study is sponsored by BeOne Medicines Ltd. Medical writing was provided by Amiculum, and supported by BeOne Medicines.

CORRESPONDENCE: Geoffrey J. Lindeman, lindeman@wehi.edu.au

Presented at SABCS, San Antonio, TX, USA, December 9-12, 2025