BREAKER-101: A Phase 1a/1b Open-Label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of BBO-10203 in Patients with Advanced Solid Tumors

Andreas Varkaris[1], Marla Lipsyc-Sharf[2], Minal Barve[3], Mateusz Opyrchal[4], Antonio Giordano[5], Erika Hamilton[6], Jordi Rodon[7], Komal Jhaveri[8], Virginia Kaklamani[9], Charlotte Lemech[10], Linda Wu[11], Rohan M. Shah[12], Joon Whan Rhee[12], Yong Ben[12], Stephen J. Luen[13]

[1]Massachusetts General Hospital, Boston, MA, USA; [2]UCLA Health, Los Angeles, CA, USA ; [3]Sarah Cannon Research Institute at Mary Crowley, Dallas, TX, USA; [4]Indiana University, Indianapolis, IN, USA; [5]Dana Farber Cancer Institute, Boston, MA, USA; [6]Sarah Cannon Research Institute, Nashville, TN, USA; [7]MD Anderson Cancer Center, Houston, TX, USA; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]University of Texas Health Science Center, San Antonio, TX, USA; [10]Scientia Clinical Research, Sydney, Australia; [11]Columbia University Irving Medical Center, New York, NY, USA; [12]BBOT, South San Francisco, CA, USA; [13]Peter MacCallum Cancer Centre, Melbourne, Australia

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Background

- Activation of phosphatidylinositol 3-kinase alpha–protein kinase B (PI3Kα/AKT) signaling induced by canonical-upstream receptor tyrosine kinase (RTK) or rat sarcoma (RAS) interaction has been implicated in resistance to hormonal and human epidermal growth factor receptor 2 (HER2)-directed targeted therapies in advanced breast cancer (aBC).[1] Although commercially available orthosteric PI3Kα inhibitors can suppress pathway activation, their clinical utility as monotherapy and in combination regimens has been hindered by a narrow therapeutic window due to on-target PI3Kα toxicities such as hyperglycemia.[2]
- Previous studies have established that RAS-mediated activation of PI3Kα plays a critical role in promoting oncogenic signaling while preserving normal cellular functions such as glucose metabolism.[3–5]
- BBO-10203 is a novel, first-in-class, orally administered, covalent small molecule inhibitor with blood-brain barrier penetration, designed to break the PI3Kα:RAS interaction and inhibit RAS-mediated activation of the PI3Kα-AKT signaling pathway while preserving the normal catalytic function of PI3Kα involved in cell growth, metabolism, and glucose homeostasis (Figure 1).[6]
- In preclinical models of HER2-positive (HER2+) aBC, BBO-10203 demonstrated potent antitumor activity as monotherapy and exhibited strong synergy when combined with HER2-directed therapies.[6] Similarly, BBO-10203 showed synergy with hormonal and cyclin-dependent kinase (CDK) 4/6 directed therapies in hormone receptor-positive, HER2-negative (HR+/HER2–) aBC models.[6,7] Notably, treatment with BBO-10203 did not result in hyperglycemia or other toxicities typically associated with PI3Kα kinase inhibition.[6,7] These findings support the further development and clinical evaluation of BBO-10203 as a therapeutic strategy for HR+/HER2– and HER2+ aBC.
- BREAKER-101 (NCT06625775) is a Phase 1a/1b study evaluating the safety, tolerability, and efficacy of BBO-10203 in patients with advanced solid tumors.

Methods

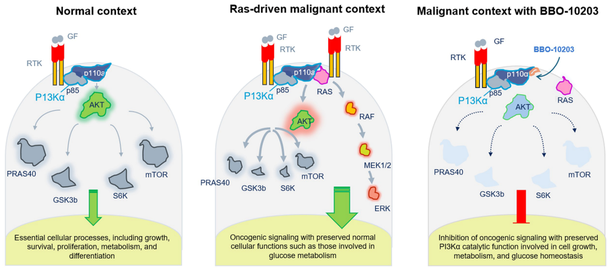
Study design

- BREAKER-101 is a first-in-human, multicenter, open-label, Phase 1a/1b study evaluating the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of BBO-10203 as monotherapy and in combination with trastuzumab, fulvestrant ± ribociclib, or FOLFOX + bevacizumab in patients with locally advanced unresectable or metastatic (ie, advanced) solid tumors.
- The study includes a dose escalation phase and an expansion phase (Figure 2).
- Dose escalation (or de-escalation) of BBO-10203 monotherapy will initially follow a Bayesian optimal interval (BOIN) design.

Patients and treatments

- BBO-10203 will be taken orally, once daily, and will be evaluated in a 21-day or 28-day treatment cycle at different dose levels depending on the cohort.
- Trastuzumab is administered as an 8 mg/kg infusion over 90 minutes on Cycle 1 Day 1, and a 6 mg/kg infusion over 30–90 minutes during subsequent cycles or 600 mg subcutaneous. Participants will receive trastuzumab as infusion or subcutaneous injection every 21 days.
- Fulvestrant is administered 500 mg by intramuscular injection every 28 days with an additional dose on Cycle1, Day 15.
- Ribociclib is administered 600 mg orally once daily (21 days on treatment, 7 days off).
- FOLFOX (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, 5FU 400 mg/m^2 + 2400 mg/m^2) is administered IV every 14 days and bevacizumab 5 mg/kg is administered IV every 14 days.

BBO-10203 mechanism of action



Abbreviations: AKT, protein kinase B; GF, growth factor; P13Kα, phosphoinositide 3-kinase alpha; RAS, rat sarcoma; RTK, receptor tyrosine kinase

Key inclusion criteria

General
Adults with locally advanced and unresectable or metastatic HER2+ aBC, HR+/HER2– advanced breast cancer (aBC), KRAS mutant aCRC, or KRAS mutant aNSCLC; measurable disease per RECIST v1.1 except for HR+/HER2– aBC ; ECOG performance status 0 or 1

HER2+ aBC cohorts
≥2 prior lines of anti-HER2-directed therapy. 1 prior line is acceptable if no other regionally available SoC

HR+, HER2– aBC, KRAS mutant aCRC or aNSCLC cohorts
Must have progression on, or disease recurrence after at least one line of SoC treatment or in the opinion of the investigator, would be unlikely to tolerate or derive clinically meaningful benefit from SoC therapy

BBO-10203 + fulvestrant combination cohort patients with HR+, HER2– aBC
Confirmed PIK3CA mutation, must have been treated with a CDK4/6i for at least 6 months

BBO-10203 + fulvestrant + ribociclib combination cohort patients with HR+, HER2– aBC
Confirmed PIK3CA mutation, no prior systemic therapy in the aBC setting permitted

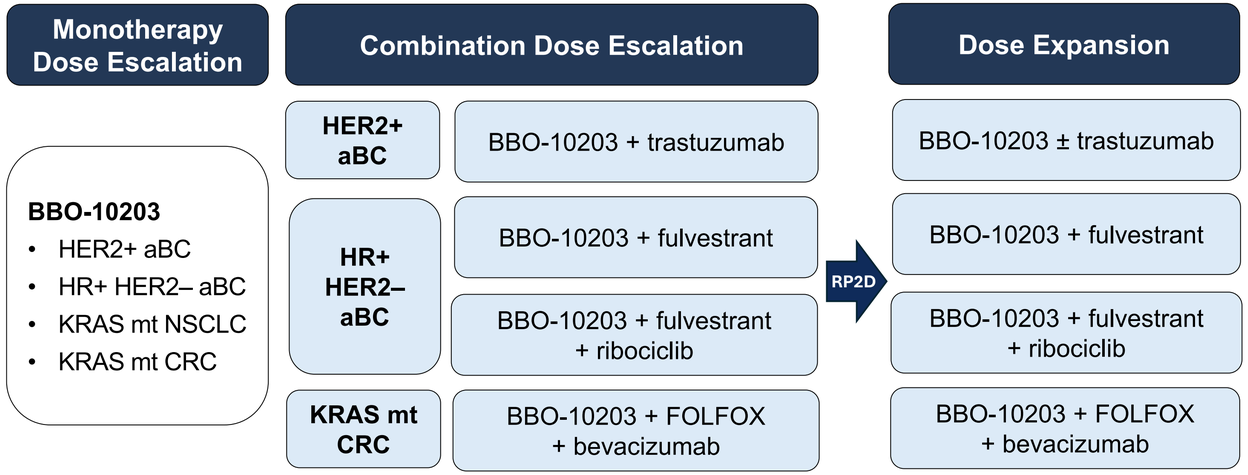
BBO-10203 + FOLFOX + bevacizumab combination cohort patients with KRAS mutant aCRC
One prior line of irinotecan-containing therapy for locally advanced or metastatic CRC is allowed

Key exclusion criteria

- Prior Pi3k/AKTi patients are excluded for dose expansion for HR+ BC
- >1 line of chemotherapy is excluded for HR+ BC
- Patients with untreated and/or non-stable brain metastases are excluded

Abbreviations: aBC, advanced breast cancer; aCRC, advanced colorectal cancer; aNSCLC, advanced non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; RECIST, Response Evaluation Criteria in Solid Tumors; SoC, standard of care

BREAKER-101 study design



Objectives and outcome measures

Objective

- To evaluate the safety, tolerability, preliminary antitumor activity, and pharmacokinetics of BBO-10203 as a single agent and in combination with trastuzumab, fulvestrant ± ribociclib, or FOLFOX + bevacizumab in patients with locally advanced unresectable or metastatic (ie, advanced) solid tumors.

Primary outcome measures

- Determination of maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of BBO-10203 as a single agent.
- Percentage of patients with treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and dose-limiting toxicities (DLTs) over ~5 years
- Recommended BBO-10203 dose in combination with trastuzumab, fulvestrant ± ribociclib, and FOLFOX + bevacizumab.

Secondary outcome measures

- Clinical benefit rate (CBR), duration of response (DoR), progression-free survival (PFS) and objective response rate (for patients with measurable disease) as assessed by RECIST v1.1, and overall survival (OS)
- Area under the concentration-time curve (AUC), maximum plasma drug concentration (Cmax) and time to maximum plasma drug concentration (Tmax)

Exploratory

- Intracranial activity of BBO-10203 will be evaluated using Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria.

Current status

- The study is enrolling patients in the United States and Australia.
- An estimated 392 patients will be enrolled.

References

1. Castel P, et al. Nat Cancer 2021;2:587–7.
2. Rugo HS, et al. Ann Oncol 2020;31:1001–10.
3. Gupta S, et al. Cell 2007;129:957–68.
4. Castellano E, et al. Cancer Cell 2013;24(5):617–30.
5. Murillo MM, et al. Cell Rep 2018;25:3545–53.
6. Simanshu D, et al. Science 2025;389:409–15.
7. Sinkevicius KW, et al. Proc SABCS 2025 (poster PS2-12-06).

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For further information contact: Rohan.Shah@bbotx.com