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

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ABSTRACT

Background: HR+/HER2− tumors account for ~70% of all breast cancers (BCs)[1] and are responsible for most BC-related deaths. CDK4/6 inhibitors (CDK4/6i) + endocrine therapy (ET) have improved outcomes for HR+/HER2− BC[2]; however, patients eventually experience progressive disease and require 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 BC, estrogen receptor signaling leads to upregulation of BCL2, which is overexpressed in 70-80% of HR+ BC.[3-5] When administered in rational combinations with other anticancer agents, BCL2 inhibitors (BCL2i) are likely to enhance potential antitumor effects.[5] In HR+ BC mouse xenograft models, 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 BCL2i + ET significantly augmented this antitumor activity, suggesting further exploration of the triplet is warranted.[7-9]

BGB-21447 is a novel, orally bioavailable, next-generation BH3 mimetic that was designed to be a highly potent inhibitor of both wild-type and mutant BCL2, which is also active against BCL-xL and is currently in clinical trials for hematologic cancers and BC.

BGB-43395 is a selective CDK4i with improved CDK4 coverage and greater selectivity for CDK4 over CDK6, thus minimizing off-target toxicities. BGB-43395 is currently under development with ET in HR+ BC and other selected solid tumors (NCT06120283, NCT06253195). Here, we describe an ongoing phase 1 study of BGB-21447 + fulvestrant with and without BGB-43395 (NCT06756932).

Methods: This is an open-label, international, multicenter, phase 1 dose-escalation study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and

preliminary antitumor activity of BGB-21447 in combination with fulvestrant without (Part A) or with BGB-43395 (Part B) in patients with previously treated HR+/HER2− metastatic BC. Sequential cohorts will receive ascending doses of BGB-21447 and fulvestrant. BGB-43395 will be added to the doublet combination dose-escalation component.

Key eligibility criteria include patients ≥18 years with histologically or cytologically confirmed HR+HER2− metastatic BC, previous treatment in the advanced/metastatic setting, including prior treatment with CDK4/6i and ET in any setting, Eastern Cooperative Oncology Group Performance Status ≤1, and adequate organ function. Patients with prior BCL2i exposure are excluded.

Primary objectives are to assess the safety and tolerability of BGB-21447 in combination with fulvestrant, with or without BGB-43395, and to determine the maximum tolerated dose, maximum administered dose, and recommended dose for expansion of both the doublet and triplet combination. Secondary objectives are preliminary antitumor activity (objective response rate, duration of response, and time to response per Response Evaluation Criteria in Solid Tumors v1.1), characterization of the PK (single dose and steady state), and the preliminary effect of food on PK.

This study is currently recruiting patients, with sites open across Australia, China, and the United States (Part A only).