Preclinical characterization of BGB-43395, a potential best-in-class CDK4 selective inhibitor with potent pharmacodynamic and anti-tumor activity in HR+HER2- breast cancer models

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ABSTRACT

Cyclin-dependent kinase (CDK) 4/6 inhibitors (palbociclib, ribociclib and abemaciclib) in combination with endocrine therapies have become the standard of care for patients with metastatic hormone receptor-positive, HER2-negative breast cancer (HR+HER2- BC). However, HR+HER2- BC is primarily dependent on CDK4, while CDK6 inhibition by dual CDK4/6 inhibitors often leads to dose-limiting neutropenia, which requires treatment holidays or dose reductions, thus limiting sustained CDK4 inhibition. Therefore, BGB-43395, a CDK4 selective inhibitor, was developed to reduce neutropenia by sparing CDK6, thereby maximizing CDK4 inhibition to further improve clinical benefit.

BGB-43395 is a highly potent CDK4 kinase inhibitor with high selectivity over CDK6 and other CDK family kinases at biochemical level. In addition, BGB-43395 also demonstrated great selectivity against a panel of 200 other kinases. These properties translated into a desirable toxicity profile in nonclinical toxicity studies, where BGB-43395 was well tolerated without concerning of neutropenia and gastrointestinal toxicity issues.

In the biochemical assay, BGB-43395 exhibits superior kinase inhibition against CDK4 compared to approved CDK4/(6) inhibitors (palbociclib, ribociclib and abemaciclib) and investigational CDK4 inhibitor PF-07220060. The potency of BGB-43395 was further determined by RB1 phosphorylation inhibition in human breast cancer cell lines. Compared to PF-07220060 and approved CDK4/6 inhibitors, BGB-43395 demonstrated more potent inhibition of RB1 phosphorylation (pRB1-S780) in CDK4-dependent HR+HER2- BC cell lines. As a result, BGB-43395 showed greater anti-proliferative activity in HR+HER2- BC cell lines as well as other cancer cell lines including prostate, ovarian, endometrial and lung cancer.

The *in-vivo* pharmacodynamic and anti-tumor activity of BGB-43395 were further evaluated in CDK4-dependent tumor models. BGB-43395 monotherapy demonstrated significant inhibition of RB1 phosphorylation in a dose-dependent manner in MCL Jeko1 and HR+HER2- MCF7 mouse xenograft tumors. BGB-43395 monotherapy treatment resulted in a greater tumor growth inhibition than palbociclib at clinically relevant dose in Jeko1 xenograft models. BGB-43395 in combination with fulvestrant also demonstrated a greater tumor growth inhibition compared to palbociclib in combination with fulvestrant in HR+HER2- MCF7 xenograft models.

In summary, BGB-43395 is a potential best-in-class CDK4 inhibitor with high potency and selectivity over CDK6 and other kinases, providing an opportunity to achieve high exposure and thus maximum on-target CDK4 inhibition for the treatment of HR+HER2- breast cancer and other CDK4 dependent cancers. BGB-43395 is currently undergoing clinical investigation as monotherapy or in combination with endocrine therapies in patients with metastatic HR+HER2- BC and other advanced solid tumors (NCT06120283).