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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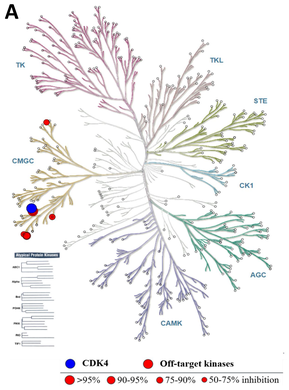
Background

- Cyclin-dependent kinase (CDK) 4/6 is a key regulator of G1/S cell cycle transition. Dual CDK4/6 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)[1,2].
- However, HR+HER2- BC is primarily dependent on CDK4. 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 [3,4].
- Therefore, BGB-43395, a CDK4 selective inhibitor, was developed to reduce neutropenia by sparing CDK6, thereby maximizing CDK4 inhibition to further improve clinical benefit.

Results

- BGB-43395 is a highly potent CDK4 inhibitor. The IC50 of BGB-43395 against CDK4 was 0.91±0.42 nM (n=3) under 100 μM ATP condition at biochemical level.
- BGB-43395 showed high selectivity over CDK6 and other CDK family kinases at biochemical level. In addition, BGB-43395 also demonstrated favorable selectivity against a panel of other kinases. These properties translated into a desirable toxicity profile in nonclinical toxicity studies, where BGB-43395 was well tolerated without concerning neutropenia and gastrointestinal toxicity issues (data not shown).
- Compared to Atirmociclib (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 of BGB-43395 was further evaluated in CDK4-dependent tumor models. BGB-43395 monotherapy demonstrated significant inhibition of RB1 phosphorylation in tumor in a dose-dependent manner in MCL Jeko1 and HR+HER2- MCF7 mouse xenograft tumors.
- BGB-43395 monotherapy treatment demonstrated significant tumor growth inhibition in the Jeko1 xenograft models. In the HR+HER2- MCF7 xenograft model and in a PDX model derived from clinical progressor on palbociclib treatment, BGB-43395 in combination with fulvestrant also demonstrated significant tumor growth inhibition.

Figure 1. BGB-43395 is a highly potent CDK4 inhibitor with high selectivity over CDK6 and other kinases



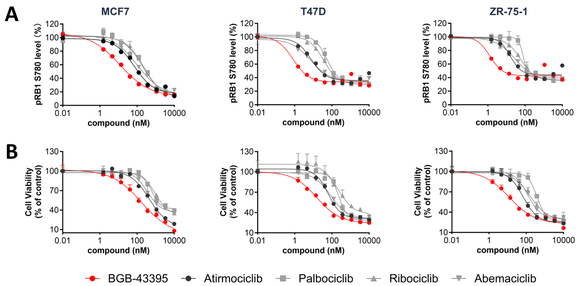
B

Target	Selectivity to CDK4 (fold)
CDK4/Cyclin D1	1
CDK6/Cyclin D3	29
CDK1/Cyclin B1	4015
CDK2/Cyclin E1	144
CDK3/Cyclin E1	280
CDK5/p35	>5882
CDK7/Cyclin H-MAT1	1606
CDK9/Cyclin T1	1965
GSK3β	1347

(A) The kinase selectivity of BGB-43395 was assessed at the concentration of 100x IC_{50} against CDK4 in a panel of 372 kinases. The IC_{50} of BGB-43395 against CDK4 was 0.91±0.42 nM (n=3) under 100 μM ATP condition measured by Reaction Biology Corp.

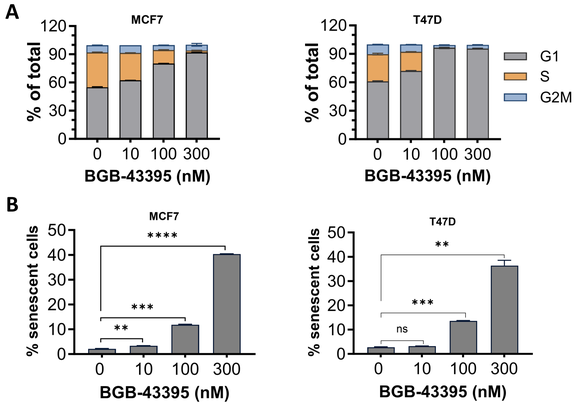
(B) The selectivity of BGB-43395 over CDKs and GSK3β under 1 mM ATP condition in biochemical assay.

Figure 2. BGB-43395 demonstrated potent pRB1 inhibition and anti-proliferation activity in HR+ BC cell lines



(A) The RB1 S780 phosphorylation inhibition activity and (B) anti-cellular proliferation activity of BGB-43395, CDK4/6 inhibitors (Palbociclib, Ribociclib and Abemaciclib) and investigational CDK4 inhibitor Atirmociclib (PF-07220060), in HR+BC MCF7, T47D and ZR-75-1 cell lines.

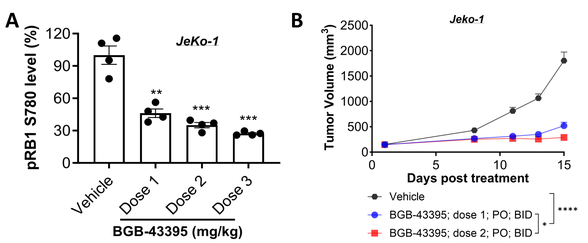
Figure 3. BGB-43395 induced G1 cell cycle arrest and cellular senescence in HR +BC cells in a dose dependent manner



(A) Cell cycle distribution of MCF7 and T47D cells treated with indicated concentrations of BGB-43395 *in vitro*.

(B) Cell senescence induced by BGB-43395 in MCF7 and T47D cells. Senescent cells were determined by β-Gal staining and analyzed by flow cytometry. ** $p<0.01$; *** $p<0.001$; **** $p<0.0001$.

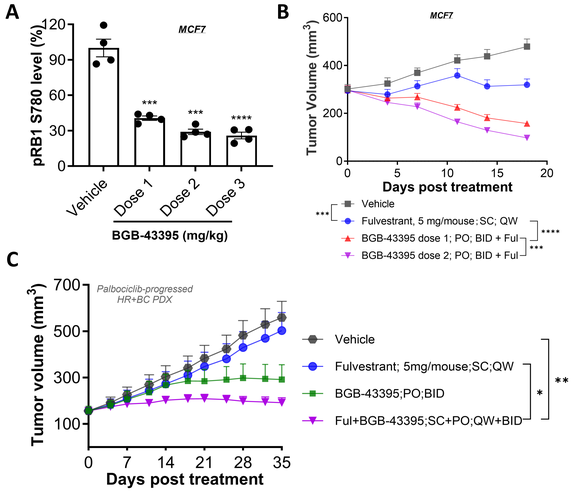
Figure 4. BGB-43395 demonstrated potent pRB1 inhibition and anti-tumor efficacy in Jeko-1 xenograft model



(A) Jeko-1 xenograft models were treated with a single dose of BGB-43395 at indicated doses, tumor samples were collected, pRB1-S780 was analyzed by a HTRF-based assay. ** p<0.01; *** p<0.001, compared to vehicle.

(B)Tumor growth inhibition by BGB-43395 monotherapy in CDK4-dependent MCL Jeko1 xenograft model. ** p<0.01; **** p<0.0001.

Figure 5. BGB-43395 demonstrated potent anti-tumor activity in naïve and palbociclib progressed HR+ BC models



(A) MCF7 xenograft models were treated with a single dose of BGB-43395 at indicated doses, tumor pRB1-S780 was analyzed by a HTRF-based assay.

(B) Tumor growth inhibition by BGB-43395 in combination with fulvestrant in HR+/HER2- MCF7 xenograft model.

(C) Tumor growth inhibition by BGB-43395 monotherapy or in combination with fulvestrant in PDX model derived from HR+BC patient who progressed on palbociclib.

** p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001.*

Summary and conclusions

- BGB-43395 is a highly potent and selective CDK4 inhibitor, with superior CDK4 potency compared with palbociclib, ribociclib and abemaciclib and atirmociclib (PF-07220060).
- The high selectivity over CDK6 and other kinases of BGB-43395 may provide an opportunity to achieve high exposure and maximize CDK4 coverage in clinical settings.
- 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, NCT06253195)[5,6].

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