Blood-Brain Barrier Transporters Limit CNS Delivery of Cdk 4/6 Inhibitor Palbociclib

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Purpose
Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults and is associated with poor prognosis. Developing effective therapies is significantly hampered by the blood-brain barrier (BBB), which limits delivery of anti-cancer agents to infiltrative tumor cells. The cyclin-dependent kinase 4 (Cdk4) pathway is hyperactivated in approximately 75% of GBM tumors. Palbociclib (PD0332991), a potent Cdk4/6 inhibitor, has remarkable efficacy in treating non-brain tumors. The purpose of this study is to determine the mechanisms limiting efficacy of palbociclib therapy in a patient-derived xenograft model.

Methods
Brain distribution studies of palbociclib were conducted in FVB wild-type (WT), and triple-knockout (TKO; Mdr1a/b(-/-)Bcrp1(-/-)) mice following escalating oral doses (10, 50, 100 or 150 mg/kg). Concentrations of palbociclib in plasma and brain were determined by LC-MS/MS. Survival studies were conducted in patient-derived primary GBM22 xenograft model in nude mice.

Results
Two hours post-dose, the brain-to-plasma ratio was constant in WT and TKO mice over a dose range of 10 to 150 mg/kg [brain-to-plasma ratio (10 mg/kg: WT: 0.15±0.06; TKO: 10.3±1.7), (50 mg/kg: WT: 0.19±0.06; TKO: 8.5±3.6), (100 mg/kg: WT: 0.17±0.02; TKO: 4.5±1.7), (150 mg/kg: WT: 0.17±0.03; TKO: 7.8±0.52)]. Consistent with sub-therapeutic delivery across the BBB, palbociclib did not prolong the median survival of an orthotopic GBM22 xenograft model. Conversely, treatment of GBM22 xenografts grown as flank tumors resulted in a significant (45 day) survival benefit. Brain concentrations following a 150 mg/kg dose were intentionally comparable to flank tumor concentrations following a 10 mg/kg dose [770±230 ng/mL and 730±510 ng/mL, respectively], and neither provided a therapeutic response.

Conclusion
These data suggest that BBB efflux transport limits the brain delivery and efficacy of palbociclib in the treatment of brain tumors such as glioblastoma. This has important translational implications in the use of palbociclib in either mono or combination therapies for brain tumors.