Brain Distribution of Ponatinib, a Multi-kinase Inhibitor: Implications for the Treatment of Malignant Brain Tumors
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Purpose
Delivery of drugs across the blood-brain barrier (BBB) is a major challenge in the treatment of malignant brain tumors, including glioblastoma (GBM). Two major efflux transporters, such as P-glycoprotein (P-gp) and breast cancer resistance protein (Bcrp), have been identified at the BBB and prevent delivery of many tyrosine kinase inhibitors. Ponatinib is a potent RET (Rearranged during Transfection) inhibitor with multi-kinase activity. The objective was to quantitatively investigate the role of BBB efflux transporters in brain delivery of ponatinib and efficacy of the drug in a GBM patient-derived xenograft that expresses RET.

Methods
In vivo animal experiments were conducted in wild-type and transgenic Mdr1a/b(-/-)Bcrp1(-/-) FVB mice to investigate the role of efflux transporters in brain delivery of ponatinib. A 30 mg/kg of ponatinib suspension was administered via oral gavage. Plasma and brain samples were harvested at several time points (0.5, 2, 4, 8, 12, 16, and 24 hours postdose; n=3-4 at each time point). Total drug concentration in plasma and brain homogenate samples were determined by LC/MS. Pharmacokinetic parameters from the resultant total drug concentration-over-time profiles were estimated using noncompartmental analysis. The estimated parameters/metrics in the wild-type and Mdr1a/b(-/-)Bcrp1(-/-) mice were compared by unpaired two-sample t-tests. Preliminary efficacy of ponatinib was tested by administering a 30 mg/kg of ponatinib suspension to GBM patient-derived xenograft mice (n=7) with an implanted flank tumor, GBM6 that expresses RET. The flank tumor growth was monitored until the tumor volume exceeded 1500mm³. The log-rank test was performed to compare the number of study days to reach the volume endpoint between the treatment and placebo groups.

Results
In vivo experiments with GBM patient-derived xenograft mice demonstrated that ponatinib significantly suppressed tumor growth compared to placebo (p-value =0.001), demonstrating efficacy of the drug in the flank tumor. The AUCplasma did not statistically differ (p-value = 0.9) between the wild-type (18.1 hour-uM) and Mdr1a/b(-/-)Bcrp1(-/-) mice (17.8 hour-uM), suggesting that efflux transporters (P-gp and/or Bcrp) have minimal effect on the systemic exposure of ponatinib. In agreement with this, the apparent oral clearance and Cmax from the plasma concentration-time profiles, respectively, were similar between the wild-type (1.6 L/hour; 1.9 uM) and Mdr1a/b(-/-)Bcrp1(-/-) (1.6 L/hour; 1.8 uM) mice. However, the AUCbrain in the Mdr1a/b(-/-)Bcrp1(-/-) mice was 18-fold higher (p-value = 0.002) compared with wild-type mice. The brain concentrations in the Mdr1a/b(-/-)Bcrp1(-/-) mice were higher than those in the wild-type mice at all postdose time points. The maximum drug concentration (Cmax) in brain was 13.6-fold higher in the Mdr1a/b(-/-)Bcrp1(-/-) mice compared with wild-type mice. At the Cmax, the mean brain-to-plasma ratio was 0.88 in the wild-type mice and 12.7 in the Mdr1a/b(-/-)Bcrp1(-/-) mice. These data support our hypothesis that efflux transporters, P-gp and Bcrp, limit the brain distribution of ponatinib, and an increased brain partitioning of the drug is possible. In the Mdr1a/b(-/-)Bcrp1(-/-) mice, the terminal half-life in plasma (5.8 hours) was similar to that in brain (5.8 hours). In the wild-type mice, the terminal half-life in plasma was shorter (3.4 hours) compared to that in brain (5.3 hours). Within each type of mouse, the Tmax values did not differ between the plasma and brain concentration-time profiles (2 hours in wild-type mice; 4 hours in Mdr1a/b(-/-)Bcrp1(-/-) mice).

Conclusion
Pharmacokinetic assessment with total drug concentrations of ponatinib suggests restriction of the drug distribution to the brain by efflux transporters at the blood-brain barrier, and an increased brain partitioning of the drug is possible. Ponatinib was shown to be effective in suppressing flank tumor growth in the GBM patient-derived xenograft mouse model. These data from our in vivo animal experiments support the merit of further evaluating ponatinib for its therapeutic potential to treat GBM. We will do this in an orthotopic model (intracranial) to examine if limited delivery via BBB efflux will also limit efficacy.