ABSTRACT CITATION ID: vdae090.095
OCT0.10
PReOPErATIVe TuCatinib IN PaTIENTS WITh HER2 amplified/mUtant breast oR oTHer sOLID TuMORS WHO requIRe Brain Metastasis reSection: A WinDow oF OPPORTUnITy sTUDY (WINHER2 sTUDY, NCt035892068)
Emanuela ferraro1, Verna solomon1, Vanessa thompson1, Rachael polliна2, Brian Pittner2, Nelson moss1, Andrew D. seidman1; 1Memorial Sloan Kettering Cancer Center, New York/NY, USA. 2Pfizer, New York/NY, USA

BACKGROUND: Tucatinib is a potent and selective HER2 tyrosine kinase inhibitor currently approved for patients with metastatic HER2-positive (+) breast (BC) or colorectal cancer (CRC). In combination, it has demonstrated significant intracranial activity in both preclinical and clinical studies. However, the variability of brain metastasis (BM) tucatinib uptake, and brain-specific mechanisms of resistance are unknown. METHODS: WinHER2 is an ongoing investigator-initiated window of opportunity study of pre-operative tucatinib for patients with HER2+ or mutant BM requiring surgery. The objective is to identify mechanisms of resistance of tucatinib in the brain. With the hypothesis that reduced tucatinib tumor penetration may limit its therapeutic efficacy, the primary endpoint is tucatinib brain drug concentration in the resected metastases, blood, and cerebrospinal fluid. The secondary objectives are the characterization of resistance mechanisms using a multi-omics approach including proteomics by immunohistochemistry and electron microscopy (efflux pump and blood brain tumor barrier analysis), genomics, and transcriptomics of the tumor and its microenvironment. The study design includes three parallel cohorts: Cohort A: patients with HER2+ BC progressing while on tucatinib (n=10); Cohort B: patients with tucatinib-naive HER2+ BC (n=10); Cohort C: patients with HER2-mutant BC, or HER2 amplified or mutant CRC/lung/gastroesophageal cancer (n=8). The main inclusion criteria are indication for craniotomy related to radiological/clinical BM progression and history of HER2+ or mutant disease. All patients receive 4 days of tucatinib at the standard dose pre-operatively. Preoperative perfusion brain MRI is included for correlations between perfusion parameters and tumor drug levels. Additionally, CNS-specific survival outcomes will be evaluated for cohorts B and C. Differences in cohorts A and B will be assessed by descriptive statistics for primary and secondary endpoints. This study aims to provide a biological basis for innovative future strategies to improve the prognosis of patients with HER2-altered BM, which currently remains poor.