BI-20. GENETIC PROFILING FOR EARLY EVEROLIMUS SENSITIVITY IN NEWLY DIAGNOSED GliOBLASTOMA PATIENTS ENROLLED ON NCCTG N057K
Daniel Ma1, Eva Galanis1, Patrick Peller1, Keith Ligon2,3, Caterina Giannini1, and Jann Sarkaria1; 1Mayo Clinic, Rochester, MN, USA; 2Dana-Farber Cancer Institute, Boston, MA, USA; 3Brigham and Women’s Hospital, Boston, MA, USA

BACKGROUND: Mammalian target of rapamycin (mTOR) signaling plays a critical role in tumor cell function and mTOR inhibitors have demonstrated promising activity in glioblastoma multiforme (GBM). Nevertheless, robust genetic predictors for sensitivity to mTOR inhibition remain elusive. As part of the biomarker discovery process, the North Central Cancer Treatment Group (NCCTG) incorporated functional imaging with 18FLT-PET/CT and focused exon sequencing into N057K, a Phase II clinical trial evaluating the mTORC1 inhibitor everolimus in combination with radiation(RT) and temozolomide(TMZ) in newly diagnosed GBM patients. METHODS: N057K began weekly everolimus one week prior to standard RT/TMZ. Patients who had >1cm3 of residual tumor were imaged with 18FLT-PET/CT before and after the initial two doses of everolimus, before initiating RT/TMZ. Imaged patients with a ΔSUVmax of >25% were classified as metabolic responders adapted from EORTC criteria for FDG-PET. Imaged patients with sufficient tumor samples also underwent immunohistochemical and focused exon sequencing analysis using the Seqwright 201 gene panel. Tertiary analysis focused on genes implicated in the PI3K/Akt/mTOR pathway (PTEN, PIK3CA, AKT, mTOR, Raptor/Rictor, S6, TSC1/2, NF1, CCND1, FGFR1/2). RESULTS: Nine patients had 18FLT-PET/CT imaging of which 4/9 had a metabolic response to everolimus alone. Six patients had sufficient tumor samples for further analysis, of which 3/6 had response. On IHC, 18FLT-PET responders had higher levels of PTEN expression and lower levels of pAKT and Ki-67 expression in comparison to non-responders. Focused exon sequencing found 1,458 coding alterations in 454 genes when compared to the reference genome. Only one 18FLT-PET responder had any genetic alterations within a PI3K/Akt/mTOR-implicated pathway, while all 18FLT-PET non-responders had multiple alterations within PI3K/Akt/mTOR-implicated pathways. CONCLUSIONS: 18FLT-PET successfully identified cohorts of patients who had robust, early metabolic responses to mTOR inhibition alone. These responders had robust PTEN expression on IHC and were less likely to have alterations within PI3K/Akt/mTOR-implicated pathways.