Proneural glioblastoma (GBM) is characterized by PDGF signaling through receptor and/or ligand overexpression or amplification. Despite this, clinical trials using the tyrosine kinase receptor inhibitor Gleevac for GBM have failed. The inability to respond to PDGFR inhibition could either be at the ligand/receptor level where the amount of ligand or receptor is sufficient to promote downstream signaling despite levels of PDGFR inhibition achieved clinically, or due to constitutive activation of downstream pathways making receptor activation less important. In addition to activation of PDGFR signaling, proneural GBMs frequently harbor alterations of tumor suppressor genes CDKN2A, PTEN and TP53. To understand if loss of these tumor suppressor genes drives tumor progression and evolution of independence from PDGF signaling, and thus therapeutic resistance, we used a combination of human and mouse proneural GBMs. Patient-derived primary cell cultures did not respond to PDGFR inhibition with reduction in proliferation when treated with Vatalanib, indicating that tumor cells were PDGF-independent and consistent with failed clinical trials. Despite reduction in receptor phosphorylation with drug treatment, no effects on downstream signaling in the PI3K and MAPK pathways were seen. Using the in vivo mouse RCAS/TVA model of proneural GBM we found that genetic knock down of PDGFR expression inhibited tumor formation and that simultaneously knocking down expression of CDKN2A, PTEN or TP53 could not eliminate the need for PDGF signaling for tumor initiation. However, loss of CDKN2A and PTEN in PDGF-driven tumors with high PDGFR expression accelerated tumorigenesis and lead to failure to respond to PDGFR inhibition by Vatalanib in vivo. We propose that PDGF signaling is crucial during tumor initiation but once loss of CDKN2A, PTEN and/or TP53 occurs during tumor evolution, constitutive activation of the PI3K and MAPK pathways occurs making tumor cells independent of upstream activation through PDGFR.