Therapeutic targeting of EGFR signaling in GBM has had largely disappointing results in the clinic. We sought to identify cell vulnerabilities that could be targeted in combination with EGFR. Using a murine model for GBM, primary patient-derived xenografts (PDXs), and human tumor tissue, we identify cellular metabolic changes as an important mechanism of EGFR resistance. Rather than acquired resistance, we observe a subpopulation of tumor cells with unique properties, including increased 3D tumor cell invasion, expression of progenitor cell markers, and altered lipid metabolism, that are uniquely poised to resist EGFR inhibition. Interestingly, this subpopulation of cells is selectively vulnerable to changes in lipid metabolism suggesting its importance in survival. Selection for this subpopulation appears specific to EGFR inhibition, as it is not conferred by inhibition of pathways downstream of EGFR, including Src, PI3K/Akt, and MAPK. In certain human tumors and GBM PDX, expression levels of lipid metabolic enzymes is high in the absence of EGFR inhibition. In these tumors enzyme inhibition conferred decreased tumor cell survival and invasion. Preclinical studies will evaluate the benefit of inhibiting lipid metabolic enzymes in PDX. These data identify specific tumor cell vulnerabilities and suggest possible strategies to target EGFR resistance mechanisms.