The epidermal growth factor receptor (EGFR), or its expression, is altered in 57% of glioma by mutation, rearrangement, altered splicing and/or focal amplification, suggesting that EGFR should be a prime target for therapy. However, attempts to therapeutically target EGFR in patients with glioma have so far failed. The fundamental reasons why EGFR inhibitors are so ineffective against glioma remain largely unknown. We used three approaches to address this question. First, we derived a range of early passage neurosphere cell lines from glioma patients. These cell lines express different forms of the mutated EGFR, including the most common alterations in glioma: the autoactivating deletion mutant EGFRvIII and the extracellular domain (ECD) point mutation A289V. Through exonic sequencing and signaling pathway analysis of these cell lines, several of which are resistant to EGFR-targeted therapeutics, we showed that activation of the ras/MEK/ERK signaling pathway led to innate resistance to EGFR-targeted drugs (to both tyrosine kinase inhibitors and EGFR-specific antibodies). Likewise, engagement of neurosphere cell lines with extracellular matrix proteins such as laminin caused resistance to EGFR-targeted therapeutics. Second, we analyzed a range of EGFR ECD cysteine mutants identified in glioma patient samples. All four mutants analyzed were found on the cell surface as inactive, preformed dimers. However, all receptor mutants had enhanced activation, as measured by autophosphorylation in response to EGFR ligands. Importantly, expression of these mutants in U87MG glioma xenografts rendered the tumors more susceptible to EGFR-targeted therapeutics than xenografts expressing wild-type EGFR. Last, we show that EGFRvIII partly mediates its tumorigenicity through promiscuous activation of other receptor tyrosine kinases, such as MET, through a FAK scaffold. Co-targeting the kinase activity of FAK significantly increased the antitumor activity of EGFR-targeted therapeutics. These studies provide new insight into the mechanisms of resistance and sensitivity to EGFR-based drugs in glioma.