Crizotinib and Erlotinib Inhibits Growth of c-Met+/EGFRvIII+ Primary Human Glioblastoma Xenografts

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Introduction

Receptor tyrosine kinases (RTK), such as c-Met and epidermal growth factor receptor (EGFR), are implicated in the malignant progression of glioblastoma. Studies show that RTK systems can co-modulate distinct and overlapping oncogenic downstream signaling pathways. EGFRvIII, a constitutively activated EGFR deletion mutant variant, leads to increased tumor growth and diminishes the tumor growth response to HGF:c-Met pathway inhibitor therapy. Conversely, activation of the c-Met pathway diminishes the tumor growth response to EGFR pathway inhibitors.

phospho-c-Met and phospho-EGFR expression in human glioblastoma clinical specimens

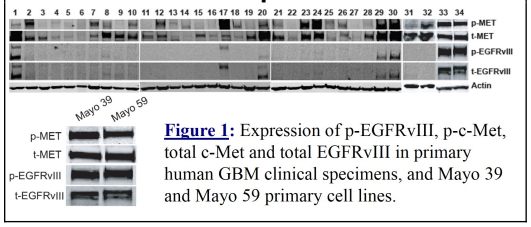

Figure 1: Expression of p-EGFRvIII, p-c-Met, total c-Met and total EGFRvIII in primary human GBM clinical specimens, and Mayo 39 and Mayo 59 primary cell lines.

Methods

Previously we reported that EGFRvIII and c-Met pathway inhibitors synergize to inhibit tumor growth in isogenic GBM cell lines engineered to express EGFRvIII. To determine the broader relevance of these earlier findings, we examined the effects of combination c-Met and EGFR pathway inhibitor therapy on tumor growth responses, downstream second messenger systems, and stem-like tumor propogating cell populations in constitutively activated c-Met+/EGFRvIII+ primary human glioblastoma xenografts lines.

Crizotinib ± Erlotinib alters tumor phgenotypes

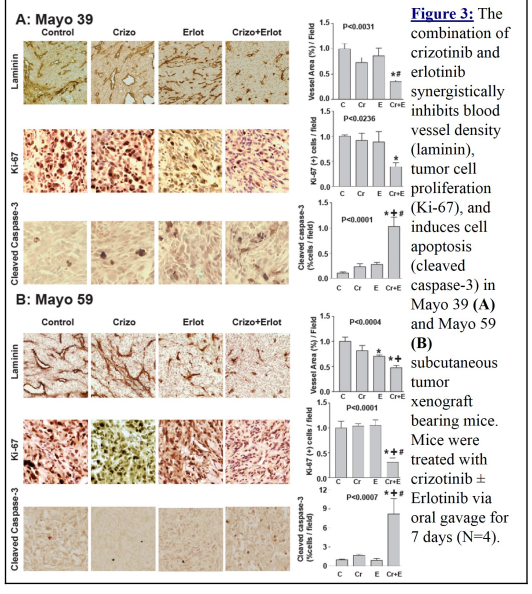

Figure 3: The combination of crizotinib and erlotinib synergistically inhibits blood vessel density (laminin), tumor cell proliferation (Ki-67), and induces cell apoptosis (cleaved caspase-3) in Mayo 39 **(A)** and Mayo 59 **(B)** subcutaneous tumor xenograft bearing mice. Mice were treated with crizotinib ± Erlotinib via oral gavage for 7 days (N=4).

Results

Crizotinib ± Erlotinib inhibits neurosphere formation

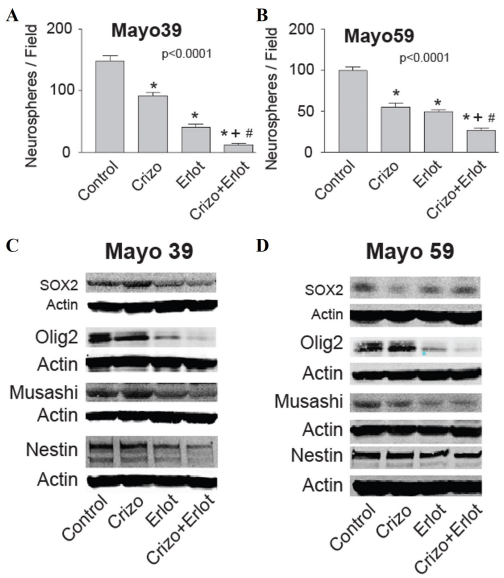

Figure 4: Targeting EGFRvIII and c-Met inhibits the formation of neurospheres derived from s.c. Mayo 39 **(A)** and Mayo 59 **(B)** human primary GBM cells and inhibits stem cell differentiation markers **(C, D).**

Conclusions

These results are consistent with and corroborate our previous findings demonstrating that targeting these two parallel pathways with c-Met and EGFR inhibitor therapy provides substantial anti-tumor activity in glioblastoma models.

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