# Targeted Inhibition of the HGF/c-Met Pathway by Merestinib Augments the Effects of Albumin-Bound Paclitaxel in Gastric Cancer

Quinn Kaurich[1], Jennifer Huang[1], Niranjan Awasthi[1,2]

[1]Department of Surgery, Indiana University School of Medicine, South Bend, IN; [2]Harper Cancer Research Institute, University of Notre Dame, South Bend, IN

**Background and Hypothesis:** Combination chemotherapy regimens are commonly used to treat gastric adenocarcinoma (GAC), but the median survival time remains less than one year. *Nab*-paclitaxel has demonstrated high antitumor activity in previous GAC studies. Many growth factors and their receptors are overexpressed in GAC and have been implicated in its pathophysiology. We hypothesize that merestinib, a small-molecule inhibitor targeting c-Met, Axl, and DDR1/2 pathways, will have significant antitumor effects and will enhance the response to *nab*-paclitaxel in GAC preclinical models.

**Project Methods:** *In vitro* proliferation and protein expression were assessed using WST-1 and immunoblot assays. Subcutaneous xenografts of MKN-45 and SNU-1 cell lines were implanted in mice to study tumor growth inhibition. Immunohistochemistry was performed to examine intratumor proliferation and microvessel density.

**Results:** *In vitro* assays showed that *nab*-paclitaxel and merestinib decreased cell proliferation in all three cell lines, with an additive effect in combination. Reduction in cell proliferation at low doses of *nab*-paclitaxel (10 nM), merestinib (100 nM), and their combination was 87%, 82%, and 94% (MKN-45 cell line, high phospho-c-Met expression), 59%, 50%, and 82% (SNU-1 cell line, low phospho-c-Met expression), and 53%, 19%, and 66% in gastric fibroblasts. Immunoblot analysis of merestinib treated MKN-45 cells revealed increased expression of apoptotic proteins and decreased expression of phospho-c-Met, phospho-EGFR, phospho-IGF-1R, phospho-ERK, and phospho-AKT. In gastric fibroblasts, merestinib decreased phospho-ERK and increased apoptotic protein expression. Phospho-c-Met and phospho-EGFR were not detected in SNU-1 immunoblots; however, phospho-ERK, phospho-VEGFR, and apoptotic protein expression increased after treatment. In MKN-45 xenografts, net tumor growth in control, *nab*-paclitaxel, merestinib, and combination groups was 503 $mm^3$, 115 $mm^3$, 91 $mm^3$, and -9.7 $mm^3$. Immunohistochemistry analysis of tumor cell proliferation and microvessel density corroborated tumor growth study results.

**Conclusion:** The data suggest that merestinib in combination with nab-paclitaxel carry a promising potential for improving clinical GAC therapy.