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### Evaluating contribution of hyperactive c-Met and ErbB signaling to tumor progression in mouse breast tumor xenografts: an *in vivo* study of c-Met and ErbB targeted therapies

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**Background:** Hyperactive c-Met signaling, including cross-talk between c-Met and ErbB family receptors, is suspected of contributing to tumor progression in a variety of cancer types. Clinical trials evaluating c-Met inhibitors alone and in combination with other targeted therapies, have produced mostly negative results in patients with amplified c-Met. This suggests other biological factors, such as c-Met and ErbB signaling activity, may be important to measure when identifying patients eligible for c-Met therapies. To measure the c-Met and ErbB signaling activity of a patient's live tumor cells, a new assay using an impedance biosensor, the CELx multi-pathway signaling function (CELx MP) test, was developed. The CELx MP test measures a patient's *ex vivo* live tumor cell response in real-time to specific ErbB and c-Met agonists to diagnose breast cancer tumors with hyperactive HER1, HER2, HER3, HER4, and c-MET signaling activity. In this study, to further elucidate the role of c-Met signaling and its potential involvement with ErbB signaling as a cancer driver, we studied *in vivo* response to a c-Met inhibitor (tepotinib), an EGFR inhibitor (erlotinib), a pan-HER inhibitor (neratinib), and a combination of these therapies using breast tumor xenograft models.

**Methods:** HCC1954, a HER2+ cell line with hyperactive c-Met and EGFR signaling and normal HER3 and HER2-driven signaling, according to the CELx MP test, was studied. Sixty 4-5-week-old female NSG mice were injected with two million cells. Mice were randomly assigned to either a control group that received Captisol or one of five treatment groups that received either neratinib, tepotinib, erlotinib, erlotinib and tepotinib, or neratinib and tepotinib for 17 days.

**Results:** The most effective treatment was the combination of neratinib plus tepotinib, where the average tumor size reduction relative to the control group was 71% ( $p=0.0003$ ). The average tumor size in the neratinib plus tepotinib treated group was 37% smaller ( $p=0.049$ ) than the neratinib treated group, and 67% smaller ( $p=0.0026$ ) than the tepotinib treated group. In the erlotinib plus tepotinib treatment group, the average tumor size was 51% smaller than the control group tumors, but the difference was not statistically significant ( $p=0.11$ ). No significant difference in tumor size was found between the control group and the erlotinib or tepotinib treated groups.

**Conclusions:** The results demonstrate that hyperactive and coincident c-Met and EGFR signaling contributes to the progression of certain breast cancers. This breast cancer sub-type is more responsive to treatment with a c-Met inhibitor plus a pan-HER inhibitor than a c-Met inhibitor plus an EGFR inhibitor or any of the single agents studied. This suggests that when hyperactive c-Met signaling and a hyperactive ErbB family member is present in a patient's tumor, each of the ErbB pathways as well as the c-Met pathway must be inhibited to treat the tumor most effectively. These findings provide strong evidence that HER2-negative breast cancer patients with coincident hyperactive c-MET and ErbB signaling may respond to treatment with a combination of pan-HER and c-Met inhibitors.