2018 ASCO Annual Meeting

J Clin Oncol 36, 2018 (suppl; abstr e24292)

Live tumor cell functional analysis and a xenograft model find co-activated c-Met and ErbB signaling in HER2-negative breast cancer

Lance G Laing, David J Burns, Salmaan Khan, Ian A MacNeil, Benjamin E Rich, Sajjad M. Soltani, Samantha Myhre, Brian F Sullivan; Celcuity Inc. Minneapolis, MN

Background: Abnormal c-Met signaling, including cross-talk between c-Met and ErbB family receptors, is suspected of playing a role in a variety of cancer types. Clinical trials evaluating investigational anti-Met/HGF therapies alone and in combination with other targeted therapies, have produced mostly negative results, however. Since subjects enrolled in these trials were primarily ones with c-MET protein overexpression or gene amplification, 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 further elucidate the role of c-Met signaling and its potential involvement with ErbB signaling as a cancer driver, a new assay using an impedance biosensor, the CELx multi-pathway signaling function (CELx MP) test, was developed. The current study set out to: 1) characterize c-Met and ErbB family signaling activity in primary HER2-negative breast tumor cells; 2) evaluate *in vivo* response to c-Met inhibitors in breast tumor xenograft models.

Methods: For the ex vivo studies, a training set of fresh tumor specimens was obtained from 74 HER2- breast cancer patients. Cell samples were cultured from each specimen. Real time live cell response to specific ErbB and c-Met agonists (NRG1b, EGF, or HGF) with or without an antagonist (pertuzumab, a HER2 dimerization inhibitor, neratinib a pan-HER kinase inhibitor, or tepotinib, a c-Met kinase inhibitor) was measured and quantified using an xCELLigence RTCA impedance biosensor (ACEA Biosciences, San Diego, CA). Signaling activity above a previously established cut-off value of 250 signaling units was used to identify abnormal levels of EGFR, HER2 and c-Met signaling activity. For the xenograft study, HCC1954, a HER2+ cell line with normal HER2 signaling, abnormal EGFR signaling, and abnormal c-Met signaling was studied. Forty female NSG mice were injected with two million cells. Mice were randomly assigned to either a control group that received Captisol or a treatment group that received neratinib, tepotinib, or neratinib and tepotinib for 16 days.

Results: Of the cell samples tested *ex vivo* with the CELx MP test, 16 of 74, (21.6%; 95% CI=14%-32%) had abnormal HER2 signaling activity, 31 of 74 (41.9%; 95% CI=31%-53%) had abnormal c-Met activity, and 17 (23.0%; CI=15%-34%) had abnormal EGFR signaling activity. For all samples tested, EGFR signaling was strongly correlated to c-Met signaling levels (r= 0.85). The average percentage of c-Met signaling activity inhibited in cell samples simultaneously agonized with NRG1, EGF, and HGF by tepotinib alone was 43% compared to 76% when tepotinib was combined with neratinib. In the xenograft study, there was no significant difference in tumor volume between the control and tepotinib-treated groups after 16 days of treatment. Tumor volumes relative to tumor size before treatment were reduced by 20% in the neratinib treated group and by 50% in the tepotinib + neratinib treated group.

Conclusions: These findings suggest that a sub-group of HER2- breast cancer patients have co-activated abnormal ErbB and c-Met signaling activity that may respond to treatment with a combination of ErbB and c-Met inhibitors.