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Sub-group of HER2- breast cancer patients with hyperactive and co-involved c-Met and ErbB pathways identified: functional signal profiling test identifies patient group that may benefit from c-Met and pan-HER combination therapy

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: Biological factors other than c-Met status, such as c-Met and ErbB signaling activity, may be important to measure when identifying patients eligible for c-Met therapies. A new assay using an impedance biosensor was developed to measure c-Met and ErbB signaling activity of live tumor cells. The CELx Multi-Pathway Signaling Function (CELx MP) Test measures an individual patient's *ex vivo* live tumor cell response in real-time to specific ErbB and c-Met agonists and antagonists to diagnose breast tumors with hyperactive HER1, HER2, HER3, and c-MET signaling. This study set out to: 1) determine the prevalence of hyperactive c-Met and ErbB family signaling amongst HER2- breast cancer patients; and 2) characterize potential cross-talk between c-Met and ErbB pathways.

Methods: For the prevalence study, fresh breast tumor specimens were obtained from 74 HER2- breast cancer patients. The amount of HER1, HER2, HER3, and c-Met for each specimen was determined using FACS. Real-time live cell response to specific ErbB and c-Met agonists (NRG1b, EGF, or HGF) alone and in combination, with or without ErbB and c-Met antagonists (2C4, a HER2 mAb dimerization inhibitor, tepotinib, a c-Met TKI, or neratinib, a pan-HER TKI) was measured using an xCELLigence RTCA impedance biosensor. From these responses, HER1, HER3, and c-Met signaling initiated by their respective agonists was quantified. The net amount of HER2 participation in EGF and NRG signaling was also quantified. Signaling activity above a previously determined cutpoint was used to identify abnormal levels of HER1, HER2, HER3 and c-Met signaling activity. For the cross-talk study, three primary HER2- breast cancer specimens with hyperactive c-Met and ErbB signaling were obtained. Response to HGF, EGF, and NRG1 alone, with or without tepotinib, was measured for these specimens using an impedance biosensor.

Results: The FACS analysis found all 74 tumor samples had normally expressed amounts of HER1, HER2, HER3, and c-Met. Of these samples, 20 of 74 (27.0%; 95% CI=18%-38%) had hyperactive c-Met signaling coincident with hyperactive signaling from at least one ErbB pathway. In each patient sample, neratinib combined with tepotinib inhibited virtually all signaling activity initiated with a combination EGF, NRG1 and HGF. In the cross-talk analysis of the three tumor samples, signaling response to EGF or NRG1 when combined with a c-Met antagonist was 9%-98% higher than signaling response measured with EGF or NRG1 alone.

Conclusions: This test found a significant sub-set of HER2- breast cancer patients with coincidental hyperactive c-Met and ErbB signaling tumors that respond *ex vivo* to a combination of pan-HER and c-Met TKI's. The unexpected increase in EGF and NRG1 signaling in the presence of a c-Met antagonist provides strong evidence that c-Met and ErbB signaling is co-involved and may explain why a c-Met TKI is not an effective antagonistic when c-Met is hyperactive for this patient sub-set. A clinical trial to evaluate treatment response of this patient sub-set to combined c-Met and pan-HER inhibitors is warranted.