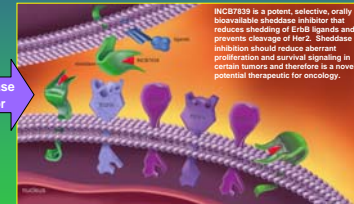
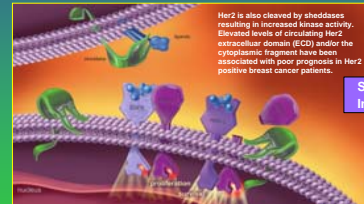
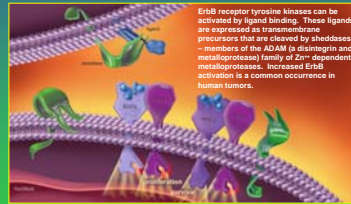


Preclinical characterization of INCB7839, a potent and selective inhibitor of ErbB ligand and HER2 receptor shedding: inhibition of ADAM10 and ADAM17 for the treatment of breast cancer

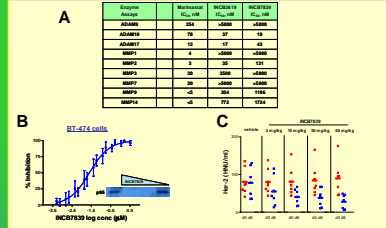
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ABSTRACT

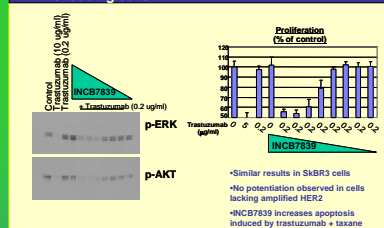
The ErbB family of receptor tyrosine kinases and the ligands that activate them are important regulators of cell proliferation, differentiation and survival. Dysregulation of this pathway occurs frequently in tumors of epithelial origin (including breast) and results in enhanced signal transduction from pathways associated with tumorigenesis and resistance to therapy. Interestingly, both the ligands that bind to the ErbB receptors (e.g. TGF and heregulin) and the HER2 receptor itself are proteolytically processed into active moieties. ErbB ligand cleavage generates a soluble, functionally active form that is critical for driving EGFR-mediated tumor cell growth and survival. Cleavage of the HER2 receptor results in the formation of a cytoplasmic fragment (p95) that possesses constitutive kinase activity and the release of an extracellular domain (ECD), which can be detected in circulation. Importantly, elevated levels of ECD and/or p95 have been associated with poor prognosis and both experimental and preliminary clinical data suggest that p95 affords resistance to trastuzumab. The enzymes responsible for these shedding events have been identified to be members of the ADAM family of metalloproteases, ADAM10 and ADAM17. Elevated ADAM activity has recently been shown to contribute to the transformed phenotype in various models of breast cancer and is associated with tumor progression. Hence, inhibition of these proteases represents a novel therapeutic strategy for the treatment of breast cancer. Toward this end, we have identified INCB7839, a potent, selective, orally bioavailable small molecule inhibitor of ADAM10 and ADAM17 which demonstrates selectivity against other metalloproteases. In xenograft models, INCB7839 effectively blocks HER2 cleavage in HER2 overexpressing human breast cancer cells in vitro and in vivo and dramatically enhances the antiproliferative effects of trastuzumab. INCB7839 also strikingly inhibits the growth of breast cancer cells lacking amplified HER2, through its effects on ErbB ligands, and potentiates the anti-tumor effects of a variety of cytotoxic, hormonal, and molecularly targeted anticancer agents. Mechanistic studies suggest that these effects are due, at least in part, to the ability of INCB7839 to reduce activation of the Akt survival pathway and increase the propensity of tumor cells to undergo apoptosis. In summary, inhibition of proteases responsible for activating ErbB pathways, through ligand and/or receptor cleavage, may offer a potentially novel and well tolerated therapeutic strategy for the treatment of human cancers. Toward testing this therapeutic hypothesis, INCB7839 is currently in clinical trials for the treatment of solid tumors.



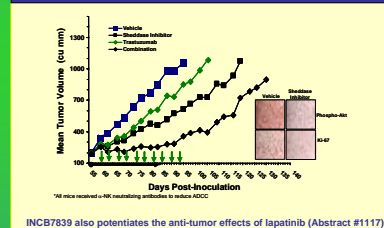
1. INCB7839 is a potent, selective ADAM10/17 inhibitor (A) that reduces HER2 ECD shedding and p95 formation in cell lines (B) and *in vivo* (C)



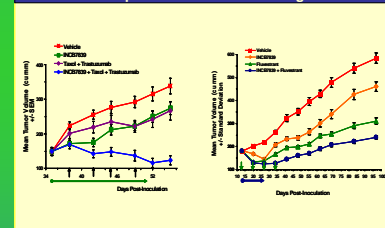
2. INCB7839 potentiates the signaling and anti-proliferative effects of trastuzumab in HER2 shedding cells



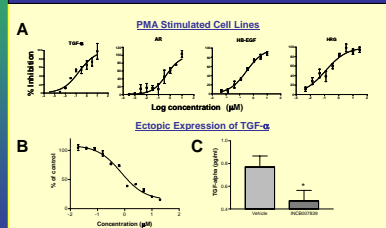
3. Inhibition of HER2 shedding synergizes with trastuzumab *in vivo* to control HER2+ disease



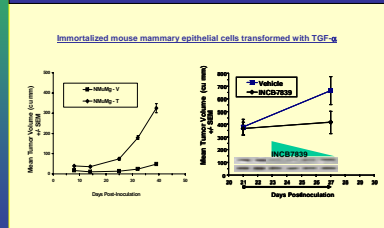
4. INCB7839 improves tumor growth control of a variety of classes of anti-cancer agents in HER2 amplified human tumor xenografts



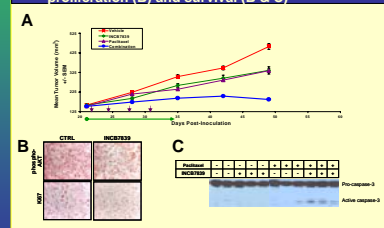
5. Selective ADAM10/17 inhibition reduces ErbB ligand shedding *in vitro* (A & B) and *in vivo* (C)



6. INCB7839 curtails ErbB ligand dependent EGFR activation and tumor growth



7. ADAM10/17 inhibition reduces ErbB mediated breast tumor xenograft growth (A) by impacting proliferation (B) and survival (B & C)



CONCLUSIONS

- A number of potent and selective ADAM10/17 inhibitors have been identified that reduce the shedding of Her2 ECD and ErbB ligands *in vitro* and *in vivo*.
- Incyte sheddase inhibitors demonstrate single agent activity and/or synergize with cytotoxic and targeted therapies in breast cancer xenograft tumor models deemed responsive to ErbB manipulation.
- INCB7839 was well tolerated at efficacious doses and does not induce the musculoskeletal side effects observed with broad-spectrum MMP inhibitors in multiple preclinical models (not shown).
- INCB7839 is currently being evaluated in the clinic (Abstract # 6064).

