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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INCB7839 is a potent, selective, orally bioavailable sheddase inhibitor that reduces shedding of ErbB ligands and prevents cleavage of Her2. Sheddase inhibition should reduce aberrant proliferation and survival signaling in certain tumors and therefore is a novel potential therapeutic for oncology.

Experimental and preliminary clinical data suggest that p95 affords resistance to trastuzumab. The enzymes responsible for ErbB activation are metalloproteases, and INCBE7839 is a potent, selective ADAM10/17 inhibitor that reduces HER2 ECD shedding and p95 formation in cell lines and in vivo.

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 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 # 6094).