ASCO University
LIFELONG LEARNING

Published on *Meeting Library* (http://meetinglibrary.asco.org)
Home > 100396-114

Neuromedin U: A potential predictive biomarker for HER2-targeted drugs.

Meeting:
2012 ASCO Annual Meeting

Category:
Breast Cancer - HER2/ER

Subcategory:
HER2+

Session Type and Session Title:
General Poster Session, Breast Cancer - HER2/ER

Abstract Number:
617

Citation:
J Clin Oncol 30, 2012 (suppl; abstr 617)

Author(s):
Sweta Rani, Serena Germano, Stephen F. Madden, Claire Corcoran, Susan Breslin, Neil A. O'Brien, Martina McDermott, Brigid Browne, Norma O'Donovan, John Crown, Lorraine O'Driscoll; School of Pharmacy and Pharmaceutical Sciences and Molecular Therapeutics for Cancer Ireland, Trinity College Dublin, Dublin, Ireland; Molecular Therapeutics for Cancer Ireland, National Institute for Cellular Biotechnology, Dublin City University, Dublin, Ireland; University of California, Los Angeles School of Medicine/Translational Oncology Research International, Los Angeles, CA; Irish Clinical Oncology Research Group and Molecular Therapeutics for Cancer, Dublin, Ireland

Background: Not all HER2-positive breast cancer patients respond to HER2-targeted drugs and some, who initially respond, subsequently relapse. There is a need to identify biomarkers for improved patient selection. Here we aimed to identify gene expression changes associated with response to HER2-targeted drugs. **Methods:** To identify mRNA changes associated with resistance, whole genome microarrays were used to profile conditioned medium (CM) from HER2-positive cell lines (SKBR3, HCC1954) and their lapatinib (L)-resistant variants (SKBR3-L^R, HCC1954-L^R). Neuromedin U (NmU) over-expression, identified in this way, was confirmed in the L-resistant cells and corresponding CM by qPCR and ELISA. Pooled data from 21 published expression datasets (n=3489 patients) was mined to relate NmU mRNA to tumour subtype and patients' outcome. NmU cDNA and siRNAs were used to over-express and knock-down expression of NmU, respectively, prior to assessing it's association with response to L, Trastuzumab (T) and Neratinib (N). **Results:** Analysis of the tumour data showed NmU expression to be particularly associated with poor outcome for patients with HER2-positive tumours (p=0.000005). In cell lines, we identified NmU mRNA and protein to be at significantly

higher levels in L-resistant cells and corresponding CM, compared to that of L-sensitive SKBR3 and HCC1954. This trend was observed for T-resistant and N-resistant SKBR3 cells ($SKBR3^{T}$, $SKBR3^{N}$) and their CM, compared to sensitive parent SKBR3 cells and CM. NmU cDNA over-expression in SKBR3 and HCC1954 increased resistance to L, T and N. Knock-down of NmU endogenous levels in $SKBR3\text{-}L^{R}$ and innately L-resistant MDA-MB-361and T47D sensitised these cells to L, T and N. Further analysis of our NmU over-expressing and knock-down cells indicated NmU to also be associated with increased motility, invasion and *anoikis* resistance. **Conclusions:** NmU expression is prognostic of poor outcome in HER2-positive breast tumours. In cell line models, NmU over-expression is associated with resistance to L, T and N. Taken together, we propose NmU as a possible prognostic and predictive biomarker for HER2-positive cancers, with potential also as a co-target to help circumvent resistance to these drugs. [SFI: 08/SRC /B1410]

Source URL: http://meetinglibrary.asco.org/content/100396-114