



Published on *Meeting Library* (<http://meetinglibrary.asco.org>)

[Home](#) > 96277-114

Effect of acquired resistance to lapatinib in HER2-positive breast cancer cells on the Bcl-2 family members MCL-1 and BAX.

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:

633

Citation:

J Clin Oncol 30, 2012 (suppl; abstr 633)

Author(s):

Alex J. Eustace, Brigid Browne, Stephen F. Madden, Lorraine O'Driscoll, Martina McDermott, Neil A. O'Brien, William Watson, John Crown, Naomi Walsh, Norma O'Donovan; National Institute for Cellular Biotechnology, Dublin City University, Dublin, Ireland; National Institute of Cellular Biotechnology and Molecular Therapeutics for Cancer, Dublin, Ireland; School of Pharmacy and Pharmaceutical Sciences and Molecular Therapeutics for Cancer Ireland, Trinity College Dublin, Dublin, Ireland; Molecular Therapeutics for Cancer Ireland, Dublin, Ireland; University of California, Los Angeles School of Medicine/Translational Oncology Research International, Los Angeles, CA; School of Medicine and Medical Science, Dublin, Ireland; Irish Clinical Oncology Research Group and Molecular Therapeutics for Cancer, Dublin, Ireland; Molecular Therapeutics for Cancer Ireland, Dublin City University, Dublin, Ireland; Molecular Therapeutics for Cancer Ireland, National Institute for Cellular Biotechnology, Dublin City University, Dublin, Ireland

Background: Lapatinib (L) is approved for the treatment of trastuzumab (T) resistant HER2 positive metastatic breast cancer. Not all HER2 positive tumors respond to L and patients who initially respond frequently relapse, due to the development of resistance to L. Understanding the molecular changes associated with L resistance may lead to the identification of targets to overcome resistance. **Methods:** SKBR3 cells were treated with either 250 nM L, or 125nM L and 5 µg/ml T twice weekly for 6 months to establish the resistant cell lines SKBR3-L and -TL. We measured by TUNEL assay the effect of L on apoptotic induction in SKBR3, -L and -TL cells. Gene array analysis of the SKBR3, -L and -TL cells identified differences in the expression of apoptosis-related genes, which were validated by immunoblotting. Finally using combinations of obatoclax (O) and L were tested in L resistant cells. **Results:** In SKBR3 cells, L (500 nM) induces

apoptosis ($15.8 \pm 2.0\%$) compared to untreated controls ($4.6 \pm 2.7\%$), whilst in SKBR3-L and -TL cells L did not induce significant apoptosis compared to controls. Gene array analysis showed that BAX mRNA is down regulated 3.2 fold in SKBR3-L cells compared to the parental cells. In SKBR3-TL cells, MCL-1 mRNA expression is increased 2.1 fold, whilst BAX mRNA is down regulated 2.1 fold compared to the parental cells. Immunoblotting confirmed that BAX protein expression was reduced in the SKBR3-L (1.5 fold, $p=0.058$) and significantly reduced in SKBR3-TL cells (2.0 fold, $p=0.039$) compared to SKBR3. MCL-1 protein expression was significantly increased in the SKBR3-L (1.6 fold, $p=0.035$) and -TL cells (2.3 fold, $p=0.031$) compared to SKBR3. Combining O (200 nM) and L (500 nM) in both SKBR3 and SKBR3-L cells produced greater growth inhibition than either drug on its own (SKBR3: $86.9 \pm 1.0\%$ vs $73.5 \pm 3.1\%$ for L ($p<0.01$) and $44.7 \pm 7.7\%$ for O, ($p<0.01$); SKBR3-L: $54.2 \pm 8.6\%$ vs $26.9 \pm 2.4\%$ for L ($p=0.027$) and $33.8 \pm 10.7\%$ for O ($p=0.04$)). **Conclusions:** Extended exposure to L in SKBR3-L and -TL cells alters the apoptotic response to L. O alone and in combination with L results in growth inhibition in L resistant cells.

Source URL: <http://meetinglibrary.asco.org/content/96277-114>