BREAST CANCER BREAKTHROUGH

TRIPLE NEGATIVE BREAST CANCER CONFERENCE 2013

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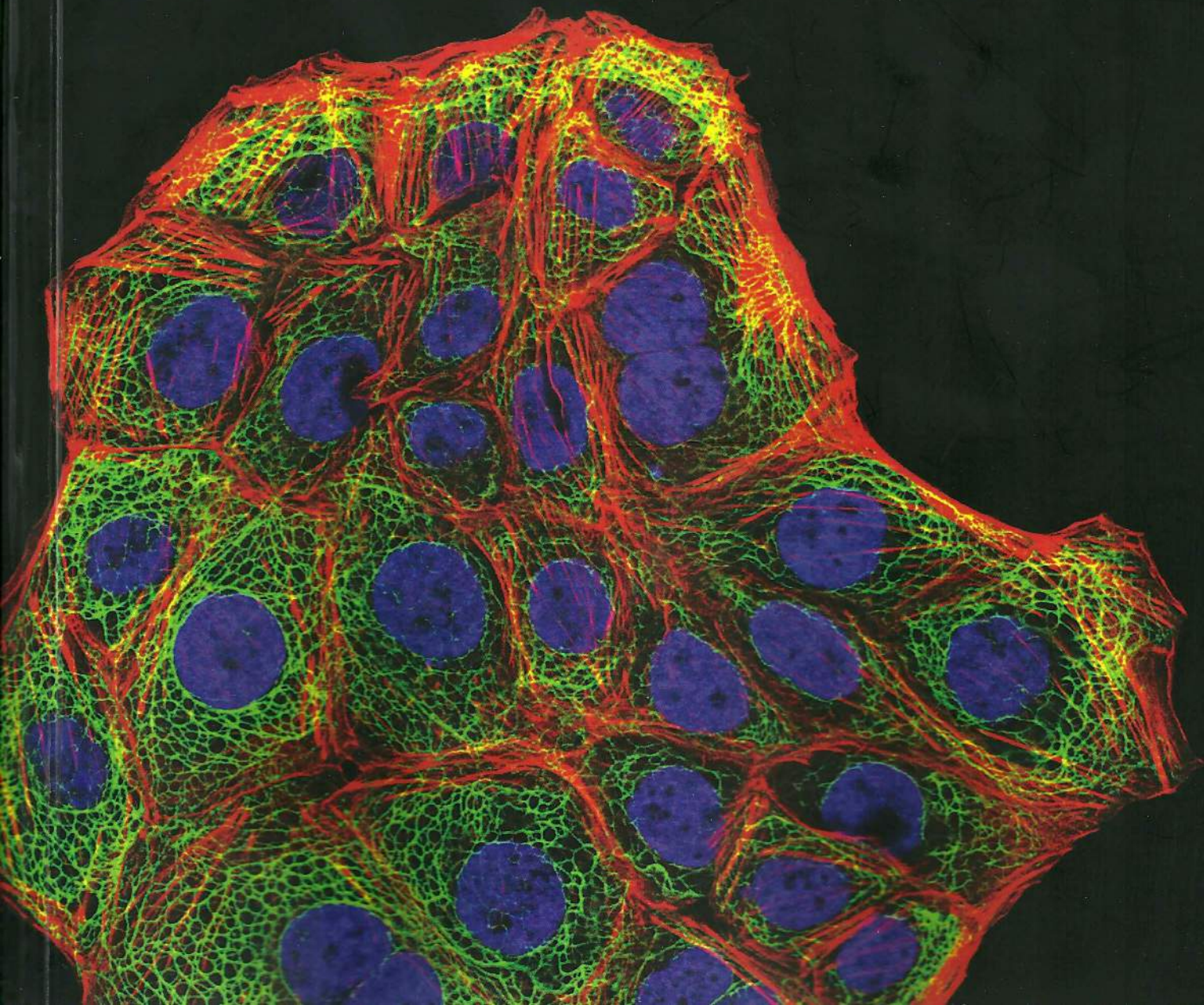

P22: Poster Walk

High throughput RNA sequencing of cetuximab resistant triple negative breast cancer

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Triple negative breast cancer (TNBC) is a sub-molecular type of breast cancer that is defined by the absence of oestrogen receptor (ER), progesterone receptor (PR) and HER2 amplification. The high expression of epidermal growth factor receptor (EGFR) in TNBC patients (60–70%) makes it a good candidate for targeted therapy. However, clinical trials have shown a poor response rate of cetuximab, an anti-EGFR antibody, as a single agent or in combination with chemotherapy in these patients. In this study, we compared the EGFR expression and cetuximab sensitivity in a panel of TNBC cell lines. Among the investigated cell lines, we found MDA-MB-468 was highly sensitive to cetuximab compare to other TNBC cell lines. Additionally, we have developed a model of cetuximab-acquired resistant TNBC, named MDA-MB-468CR, which was resistant to cetuximab in comparison to the parental MDA-MB-468 cell line. Resistant cells were morphologically similar to parental MDA-MB-468 cells with a slight increase in their growth rate. Using a next generation RNA sequencing approach, we compared the transcriptome of MDA-MB-468CR and MDA-MB-468 TNBC cells to identify the deregulated genes and pathways that might be involved in the development of cetuximab resistance. We identified 1476 genes (71.47% up-regulated and 28.52% down-regulated, FDR<0.05) that were significantly differentially-expressed between the parental and resistant cell lines. Up-regulated genes were clustered into several pathways including; p53 signaling pathway, ErbB signaling pathway, Cell cycle, TGF-beta signaling pathway and apoptosis. Moreover, we found a down-regulation in EGR1 gene, which is suggested as a cancer suppressor gene. We then correlated our findings with the public dataset from TNBC patient that have been treated with cetuximab. In conclusion, our preliminary data indicated an up-regulation of several pathways in cetuximab-acquired resistant cells that might be responsible for the development of this resistance and suggested further studies of these activated pathways in order to find different drug combinations to overcome the resistant mechanisms.

P23: Poster Walk

A proof-of-concept study of ABT888 plus carboplatin with GDC-0980 or GDC-0941 to control TN tumors

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Background: PARP is a promising target in TNBC. The PI3K pathway, in addition to its pro-proliferative effects on tumor cells, also controls the repair of DSB *(Kumar, 2010; Friedman, 2009; Juvekar, 2012; Ibrahim, 2012).*

Purpose: We hypothesize that a node-specific inhibition of PI3K pathway by GDC-0980 (dual PI3K-mTORi) or GDC-0941 (pan PI3Ki) in the presence of carboplatin would result in an enhanced impairment of DSB-repair, and subsequent sensitization to PARPi. This effect occurring simultaneously with the inhibition of classical PI3K-mTOR survival signals, will induce a robust anti-proliferative/pro-apoptotic signals in BRCA-competent TNBC cells.

Methods: We tested the in vivo efficacy of a combination of GDC-0980 (G) or GDC-0941 with