## Thursday, 17 April 2008 08:00–08:45

EUROPA DONNA TEACHING LECTURE

# Young women and fertility in breast cancer

**190** Invited

**Young women and fertility in breast cancer**

S. Loibl[1]. [1]*GBG Forschungs GmbH, Medicine and Research, Neu-Isenburg, Germany*

**Background:** 15% of all breast cancers are diagnosed in women with fertility potential. Adjuvant chemotherapy in premenopausal women with breast cancer may induce premature ovarian failure which results in amenorrhea and affects fertility.

**Results:** Chemotherapy induced amenorrhea (CIA) is strongly related to the age of the patient, the duration and amount of chemotherapy given. The incidence of CIA resulting from taxane (T) based therapy is poorly characterized. A retrospective survey in premenopausal women determined the rates of CIA in women receiving AC followed by T compared with AC alone. Older age and the addition of a taxane to AC increased the risk of CIA.

There are several options available for fertility preservation for young women who wish to have a biologic child after breast cancer and are at increased risk for infertility. Options include cryopreservation of embryos, oocytes, ovarian tissue prior to treatment, and ovarian suppression through chemotherapy. However, most of these are considered experimental with the exception of cryopreservation of embryos. There has been concern that pregnancy after breast cancer may worsen prognosis in light of the endocrine manipulations used to treat breast cancer, particularly for women with hormone sensitive disease. Several studies addressing the potential risk of pregnancy after breast cancer have not revealed any negative effect on prognosis.

Ovarian stimulation as prerequisite for embryo or oocyte preservation leads to an increased estradiol level. Letrozole in combination with FSH resulted in significant lower peak estradiol levels than anastrazole combined with FSH and standard stimulation protocols, but in a similar fertilization rate.

The administration of GnRH agonists to women with Hodgkin's disease, breast cancer, and other malignancies, has demonstrated lower rates of premature ovarian failure in patients than in nonrandomized controls. Prospective, randomized studies are ongoing, the German ZORO trial in hormone receptor negative breast cancer has finished recruitment. A recent meta-analysis found that the administration of a GnRH agonist, in addition to chemotherapy, to patients with breast cancer was associated with less recurrence and superior survival.

**Conclusion:** There are several options but no standard for fertility preservation for women at risk for CIA. However, patients need to be informed about the risk and benefits of the ovarian function preserving modalities.

## Thursday, 17 April 2008 09:00–10:30

KEYNOTE SYMPOSIUM

# New tools for developing smarter drugs

**191** Invited

**Identification of biomarkers of therapy response using functional genetic approaches**

R. Bernards[1]. [1]*The Netherlands Cancer Institute, Division of Molecular Carcinog. H-2, Amsterdam, The Netherlands*

**Background:** Unresponsiveness to therapy is remains a significant problem in the treatment of cancer, also with the new classes of targeted therapeutics. In my laboratory, we use functional genetic approached identify biomarkers that can be used to predict responsiveness to clinically-relevant cancer therapeutics. We focus on the well-established targeted cancer drugs such as Trastuzumab. This drug targets a specific molecule (HER2) that is over-expressed or in breast cancer. Nevertheless, it remains poorly explained why a significant number of tumors, which express the drug target, do not respond to the therapy. We aim to elucidate the molecular pathways that contribute to unresponsiveness to targeted cancer therapeutics using a functional genetic approach. This will yield biomarkers that can be used to predict how individual patients will respond to specific drugs. Furthermore, this work may allow the development of drugs that act in synergy with the established drug in the treatment of cancer.

**Material and Methods:** To identify biomarkers that control tumor cell responsiveness to cancer therapeutics, we use both genome-wide gain-of-function genetic screens (with cDNA expression libraries) and genome wide loss-of-function genetic screens (with RNA interference libraries) in cancer cells that are sensitive to the drug-of-interest. We search for genes whose over-expression or whose down-regulation in cultured cancer cells confers resistance to the drug-of-interest. Once we have identified such genes, we ask if their expression is correlated with clinical resistance to the drug-of-interest using tumor samples of cancer patients treated with the drug in question, whose response to therapy is documented.

**Results:** We have used BT474 human breast cancer cells (HER2 amplified), to find genes whose suppression confers resistance to Transtuzumab. We found that of 8,000 genes surveyed, only loss of PTEN caused resistance to Trastuzumab. In a cohort of 55 breast cancer patients, both loss of PTEN and mutation of the PIK3CA gene (which is controlled by PTEN) were predictive for poor response to Trastuzumab.

**Conclusion:** This study illustrates the power of genetic screens to identify biomarkers useful for predicting treatment response in the clinic. Our data demonstrate that activation of the PI3K pathway (caused either by loss of PTEN or by activating mutations in the PIK3CA gene) is predictive for poor responses to Trastuzumab-based therapy. Assessment of PI3K pathway activation in HER2+ breast cancer may help identify those patients that may benefit from drugs that inhibit the HER2 signaling pathway more downstream, e.g. by using PI3K inhibitor drugs or mTOR inhibitor drugs.

**192** Invited

**Gene expression profiling**

C. Sotiriou[1], P. Dinh[1]. [1]*Institut Jules Bordet, Chemotherapy Unit, Brussels, Belgium*

With the advent of microarray technology, unprecedented opportunities have become available for performing comprehensive molecular and genetic profiling of breast cancer. This has resulted in a) a new molecular classification of breast cancer into clinically relevant subtypes b) various molecular "prognostic" signatures that have performed, as well as, if not better than traditional clinico-pathological prognostic factors in predicting clinical outcome and c) a number of molecular "predictive" signatures that bear the exciting promise of being able to identify subsets of patients who are particularly sensitive to a given drug or regimen of drugs. Perhaps reflecting similar oncogenic pathways, the different molecular signatures, in fact, carry very similar prognostic information despite having very few overlapping genes. Although the biological role of individual genes remains largely unclear, recent work suggests that those involved in proliferation and the cell-cycle may be the common driving force behind these signatures. Also recently, epithelial-stromal interactions are being increasingly recognized as important in breast cancer development where breast tumor stromal cells have been shown to also display altered gene expression. Similar to the molecular signatures of breast cancer cells, the stromal cell and immune response signatures have been correlated with clinical outcome. Thus, gene expression profiling is an important evolving tool not only for refining prognostication, for improving patient selection but also for understanding the tumor microenvironment and the processes underlying dissemination.

**193** Invited

**Targeted imaging**

Abstract not received.

**194** Invited

**Targeting breast cancer stem cells**

K. Polyak[1], M. Shipitsin[1], N. Qimron[1], L. Campbell[1], J. Yao[1]. [1]*Dana-Farber Cancer Center, Department of Medical Oncology, Boston, USA*

**Background:** Breast cancer is a heterogeneous disease including multiple tumor subtypes associated with distinct clinical outcomes. Besides the high degree of inter-tumoral variability significant intra-tumoral heterogeneity also exists that likely contribute to therapeutic resistance and recurrence. Understanding the molecular basis of breast tumor heterogeneity is key for the development of targeted cancer preventative and therapeutic interventions. Current hypotheses explaining breast cancer diversity are the cancer stem cell and the clonal evolution models.

**Material and Methods:** To characterize cells with stem-like characteristics, we determined the gene expression, genetic, and epigenetic