Gene expression profiling can predict pathological complete response (pCR) to anthracycline-based therapy in estrogen-receptor (ER) negative breast cancer (BC) patients

Desmedt C[1], André F[2], Azambuja E[1], Haibe-Kains B[1], Larsimont D[1], D'Hondt V[1], Di Leo A[3], Piccart M[1], Pusztai L[1], Sotiriou C[4] on behalf of the investigators of the TOP trial and the Institut G Roussy /MD Anderson studies

[1]Institut J. Bordet, Université Libre de Bruxelles, Belgium; [2]Institut Gustave Roussy, France; [3] Hospital of Prato, Prato, Italy; [4]MD Anderson Cancer Center, Texas

Background

- Breast cancers show variable sensitivity to anthracycline (A)-based therapy.
- It has repeatedly and consistently been shown that the estrogen receptor (ER) is the most dominant factor influencing the molecular composition of breast cancer, defining different types of BC disease
- There exists a confounding effect of indirect ovarian suppression in ER+ BC
- Preoperative treatment followed by surgical resection of the cancer provides an excellent opportunity to correlate baseline molecular markers measured in a diagnostic needle biopsy with subsequent response to treatment.

Study Aim

1/ We aimed to identify gene expression profiles associated with pathological complete response (pCR) in ER-negative patients.

2/ We aimed to evaluate the value of the molecular targets of anthracyclines (TOP2A & CHD1) in predicting response in these ER-negative patients.

Patients

Series	*Characteristics*	*Drug regimen*	*Nr of patients*	*Nr of pCR*
TOP	International multicentric prospective trial	Epirubicin single-agent	62	11
IGR	Retrospective selection	FEC	41	19
MDACC	International multicentric prospective trial	FAC	27	5

Methods

·Gene expression profiling was done using the Affymetrix HG-U133A and Plus chips

·Ingenuity Pathways (www.ingenuity.com) was used for functional analysis

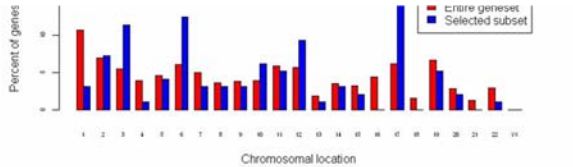
·Use of a model selection procedure based on cross-validation error estimation in order to select the genes that are able to predict significantly and specifically one of the molecular targets (TOP2A: 201291_s_at and CHD1: 204258_at) to define the indices.

·The prognostic value of genes was evaluated in a set of publicly available ER-negative tumors from systemically untreated BC patients.

Results

1. Class comparison:

- A student t-test was performed and identified 102 genes that were significantly associated with pCR across these the 3 populations (p<.01).
- 14 of these genes were located on the TOP2A amplicon



- Functional analysis of these 102 genes

Main Functions	Genes
Cell Death	FAS, ITPR2, HLA-DRB4, BNIP3L, CSNK1A1, EWSR1, BAX, LGALS3BP, MAP3K11, IFNGR1, FKBP8, HNRPA1, ABCC5, CCND3
DNA replication and recombination	TPD52L1 (includes EG:7164), FAS, PARG, KPNA2, REPIN1, BAX, IFNGR1, HNRPA1, CDC5L
Molecular Transport	NPC2, FAS, KPNA2, BAX, NPY2R, ABCA2, SFTPC, IFNGR1, SNTB1, ABCC5
Small molecule biochemistry	NPC2, SLC9A3R1, PARG, FAS, BAX, NPY2R, ABCA2, SFTPC, SNTB1, ABCC5
Cell morphology	EWSR1, SLC9A3R1, FAS, BAX, KIRREL, MAP3K11, TRIO, CCND3

- None of these genes were associated with prognosis in the untreated patients

2. Evaluation of the molecular targets of anthracyclines:

- Definition of the molecular indices for TOP2A and CHD1
  - TOP2A index= 20 genes*
  - CHD1 index= 11 genes*

*Genes which correlated with one of the prototypes of the hallmarks of breast cancer (HER2, ESR1, AURKA, STAT1, PLAU) were excluded.

- Subgroup analysis revealed that TOP2A gene and index was predictive of pCR in ERBB2+ but not ERBB2- subgroup

Genes

ERBB2+ subgroup

	coef	se(coef)	Wald z	p	n
Intercept	−1.537	0.564	−2.726	6.4E−03	38
ESR1	0.581	0.521	1.116	2.6E−01	38
ERBB2	−0.203	0.509	−0.398	6.9E−01	38
STK6	−0.145	0.757	−0.191	8.5E−01	38
PLAU	−0.521	0.607	−0.860	3.9E−01	38
STAT1	0.571	0.648	0.881	3.8E−01	38
TOP2A	1.619	0.770	2.104	3.5E−02	38
CHD1	−0.328	0.599	−0.547	5.8E−01	38

ERBB2- subgroup

	coef	se(coef)	Wald z	p	n
Intercept	−1.217	0.281	−4.328	1.5E−05	93
ESR1	0.267	0.320	0.836	4.0E−01	93
ERBB2	−0.031	0.355	−0.087	9.3E−01	93
STK6	0.035	0.433	0.081	9.4E−01	93
PLAU	−0.050	0.278	−0.179	8.6E−01	93
STAT1	0.429	0.379	1.132	2.6E−01	93
TOP2A	0.008	0.490	0.016	9.9E−01	93
CHD1	−0.056	0.339	−0.164	8.7E−01	93

Indices

	coef	se(coef)	Wald z	p	n
Intercept	−1.635	0.651	−2.514	1.2E−02	38
ESR1	0.290	1.230	1.872	6.1E−02	38
ERBB2	−2.533	1.181	−2.144	3.2E−02	38
STK6	1.081	1.011	1.069	2.8E−01	38
PLAU	1.592	0.990	1.607	1.1E−01	38
STAT1	−0.211	0.674	−0.314	7.5E−01	38
TOP2A	2.949	1.438	2.050	4.0E−02	38
CHD1	−1.826	0.981	−1.862	6.3E−02	38

	coef	se(coef)	Wald z	p	n
Intercept	−1.229	0.291	−4.228	2.4E−05	93
ESR1	0.260	0.328	0.768	4.4E−01	93
ERBB2	0.048	0.344	0.141	8.9E−01	93
STK6	0.333	0.776	0.429	6.7E−01	93
PLAU	−0.072	0.477	−0.152	8.8E−01	93
STAT1	0.334	0.383	0.873	3.8E−01	93
TOP2A	0.017	0.549	0.031	9.7E−01	93
CHD1	−0.036	0.348	−0.103	9.2E−01	93

Conclusions

These results suggest that a group of genes can identify ER-negative BC pts likely to respond to anthracyclines. These results are being further evaluated on a larger cohort of patients