ER-pathway activity as a predictive biomarker for neo-adjuvant endocrine therapy: Results of the TEAM II A trial

Introduction
Response to endocrine therapy depends on the presence of an active tumor driving ER signalling pathway and, in the case of treatment with aromatase inhibitors (AI), also on aromatase-induced estradiol as the pathway activating ligand.

Conventional nuclear staining for ER is not necessarily indicative of an estradiol-activated ER signaling pathway. We evaluated a recently described diagnostic computational model which identifies ER-pathway activity based on tissue-derived target gene mRNA levels, for its clinical utility to predict neoadjuvant AI response in ER-positive breast cancer patients.

Estrogen Receptor pathway model
We have built a Bayesian network model of the ER transcriptional program, which interprets the pathway target genes’ mRNA levels (from Affymetrix HG-U133Plus2.0 arrays) and infers the pathway target genes’ mRNA levels (from the pathway target genes’ mRNA levels, for its clinical utility to predict neoadjuvant AI response in ER-positive breast cancer patients.

Materials and Methods
Patient samples
Tumor tissue from pre-treatment biopsies and post-treatment resection material was collected from patients with early breast cancer (>2 cm and >50% ER expression) participating in the TEAM-II A trial, who were treated with neoadjuvant exemestane for 3 to 6 months, with mean treatment duration of 174 days, ranging from 86 to 288 days.

Inference of ER activity
Using Laser Capture Microdissection (LCM), tumor cells were isolated and the probability of ER-pathway activity was assessed with RT-qPCR. In total, 105 FFPE samples were analyzed (49 biopsies + 50 resection cases, of which 28 were matched). In a preliminary analysis, results were correlated with clinical response based on palpation and mammography.

Results
ER-pathway activity significantly decreased during therapy

3 months
CR PR SD PD
mean activity 0.59 0.48 0.53 0.16
std. dev. 0.19 0.28 0.23 0.11
1-sided t-test p-value CR/PR vs SD = 0.004
End of therapy
CR PR SD PD
mean activity 0.59 0.58 0.29 0.12
std. dev. 0.19 0.28 0.23 0.11
1-sided t-test p-value CR/PR vs SD = 0.004
Correlation with Ki67
Pre- and post-therapy ER activity was also correlated to the change in Ki67, expressed as remaining activity after therapy. A weak correlation (R²=0.12) was observed between pre-treatment activity and percentage of remaining Ki-67 activity, suggesting that other factors influence overall outcome of neo-adjuvant therapy.

Baseline ER-pathway activity in biopsy predicted therapy outcome after 3 months, based on mammography

Probability that ER-pathway is active
non responder responder
sample size 6 12
mean activity 0.71 0.44
std. dev. 0.17 0.24
1-sided t-test p-value = 0.007

Conclusions
• The significantly lower average baseline activity in patients with progressive disease indicates that low ER-pathway activity could be used to predict low response rates.
• This is supported by the observation that all progressive disease cases at end of therapy had low baseline ER activity.
• Furthermore, baseline activity particularly predicted early radiological response based on mammography.

These preliminary results indicate that this ER-pathway activity computational model could be able to predict response to endocrine neoadjuvant therapy. For further use, the model will be optimized and prospectively validated in an independent study.

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