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Expression of the 21 genes in the Recurrence Score assay and tamoxifen clinical benefit in the NSABP study B-14 of node negative, estrogen receptor positive breast cancer

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Background: The 21 gene Recurrence Score (RS) assay (Oncotype DX) has been validated to quantify the risk of distant recurrence in tamoxifen (tam)-treated pts with N-, ER+ breast cancer. To determine whether the RS assay predicts prognosis, response to tamoxifen, or both, we studied the pts randomized to placebo and tam in NSABP B-14.

Methods: Pts were eligible if tumor blocks were available and contained at least 5% invasive cancer. Expression was quantified by the pre-specified 21 gene RT-PCR assay, and the RS was calculated by the pre-specified algorithm. Cox models were used to evaluate the association between potential predictive variables and distant-recurrence free survival (DRFS).

Results: There were 645 evaluable pts (355 placebo and 290 tam). A subset of individual genes (Cyclin B1, Survivin, MYBL2, STK15, Ki-67, PR, and GSTM1), the proliferation gene group score and the RS were significantly associated with DRFS in the placebo pts ($p < 0.05$). ER was not associated with DRFS in the placebo pts ($p = 0.30$), and was not prognostic. In analysis of both arms, the test for interaction of tam treatment and ER was highly significant ($p = 0.0007$), indicating quantitative ER expression predicts tam benefit. The test for interaction of tam treatment and PR was not significant ($p = 0.64$). The absolute and relative tam benefits for each RS risk group are in the Table below. In contrast to quantitative ER expression which is only predictive of tam response, the 21 gene RS assay is both prognostic and predicts the response to tamoxifen.

Conclusions: Not all ER + pts benefited equally from tamoxifen. The largest benefits of tamoxifen were observed with high quantitative ER and low RS, while smaller benefits were observed with low quantitative ER and high RS.

RS Groups (645)	Placebo 10 yr DRFS (95%CI) (355)	Tamoxifen 10 yr DRFS (85%CI) (290)	Abs Benefit of Tam at 10 yrs	P- value
Low Risk (RS<18) (313)	85.9% (80.5%, 91.4%) (171)	93.1% (88.8%, 97.5%) (142)	7.2%	0.039
Int Risk (RS 18-30) (154)	62.2% (51.1%, 73.2%) (85)	79.5% (69.6%, 89.5%) (69)	17.3%	0.02
High Risk (RS≥31) (178)	68.7% (59.1%, 78.2%) (99)	70.3% (59.8%, 80.7%) (79)	1.6%	0.82