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Predictive utility of progesterone receptor (PR) and multigene expression in identifying benefit from adjuvant doxorubicin plus cyclophosphamide (AC) or docetaxel (AT) in intergroup trial E2197

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Background: Although E2197 showed no difference in recurrence or overall survival, an exploratory analysis suggested differential benefit for AC in PR-pos disease and AT in PR-neg disease (Proc ASCO 2005, abstr 512) when PR was determined in local labs. We evaluated the predictive utility of PR protein expression by IHC in a central lab and quantitative RNA expression by RT-PCR for 371 genes (including the 21-gene recurrence score [RS]) in a representative sample of 734 patients who received at least 3-4 treatment cycles.

Methods: Individual gene by treatment interactions were tested in Cox models for relapse-free interval (RFI). Permutation methods were used to control the false discovery proportion at <10%. Supervised principal components (SPC) was used to combine genes into an interaction predictor, which was evaluated via cross-validation (CV).

Results: PR Analysis. There was a weak benefit for AT in PR-neg (AT vs AC hazard ratio [RR]=0.75; p=0.06) and AC in PR-pos disease (RR=1.37; p=0.05) by central IHC (Allred score > 2 positive) but not when genomic PR was evaluated by RT-PCR (> 5.5 units positive). RS and New Genes. There was little evidence that gene expression identified AT vs. AC benefit in the hormone receptor (HR)-neg, or HR-pos, RS < 18 subsets. In contrast, there were many genes that strongly predicted differential AT vs AC benefit in the HR-pos, RS > 18 subset; SPC analyses of a multigene model suggest a significant effect (CV continuous interaction permutation p=0.03), with the AT vs. AC RR in the highest and lowest third of the SPC values estimated in CV to be 0.23 and 2.48. Oncotype DX RS did not predict differential AC vs AT benefit in HR-pos disease.

Conclusions: PR protein expression may identify a potentially clinically relevant association for differential taxane benefit, but requires validation in other datasets. A genomic classifier predicting differential benefit was identified in HR-pos tumors with a RS > 18, and if externally validated, might be useful in defining differential benefit in patients with HR-pos disease.

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