[S3-02] Molecular predictors of outcome on adjuvant CAF plus tamoxifen (T) vs T in postmenopausal patients (pts) with ER+, node+ breast cancer – Transcriptome expression analysis of the phase III trial SWOG-8814

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BACKGROUND: In SWOG-8814A, pts with ER+ node+ breast cancer and low 21 gene recurrence scores (RS) had good prognosis and no CAF benefit, but high RS predicted longer survival from CAF followed by T (CAF-T) vs T (Albain, Lancet Oncol 2010). The aims of SWOG-8814B were to identify novel genes and networks for 1) prognosis of early and late relapse and 2) prediction of CAF benefit, using whole transcriptome expression analysis with next generation RNA sequencing (NGS).
METHODS: Stored RNA previously extracted for SWOG-8814A (T, CAF-T arms; T, 5 yrs) was analyzed for RNA/library yield (see companion abstract Cherbavaz et al. for methods). Genes were sequenced and expression of mRNA species was related to disease-free survival (DFS) using Cox proportional hazards. Discovery analyses controlled false discovery rate (FDR) at 10%. Genes were identified for prognosis on T and prediction on CAF-T vs T. Networks of genes/pathways were explored. Early (0-5 yrs) and late (5-13+ yrs) time periods were studied. Gene Ontology, Cytoscape, pathway and hierarchical clustering were used for functional gene and metagene analyses.
RESULTS: Of 367 samples, 354 (96%; 142 T, 212 CAF-T; 141 DFS events) had sufficient RNA/library yield, with 20,101 genes sequenced. For prognosis on T, there were 2327 and 568 genes discovered in early and all-yrs follow-up, with only 9 genes prognostic after 5 yrs. Prognosis analyses for residual risk after CAF-T were uninformative. Functional mapping found that genes prognostic for worse DFS were enriched for proliferation (G2M, M-phase), cellular metabolism, DNA repair, stress response and EMT; whereas, those with better DFS involved transcription regulation/repression via zinc finger proteins. Hierarchical clustering (T arm) found significant DFS prognostic metagene signatures for ER-related genes, immune response, ECM/stroma, chromatin remodeling-transcription factor activity and TGFb pathway. All varied for early vs late DFS events. For example, low ER/high stroma expression signatures correlated with high proliferation gene expression and were strongly associated with early events (standardized [st] HR 2.94, $p<0.001$). Late recurrence was associated with high proliferation, both individually (stHR 1.51, $p=.035$) and in combination with higher ER expression (stHR 1.51, $p=0.09$). Fifteen genes predicted CAF benefit (9 better DFS, 6 worse), or 129 genes if FDR relaxed to 20%. Cluster analysis for CAF prediction is ongoing.
CONCLUSIONS: Unique genes, clusters and pathways were identified by NGS of archival material in ER+ N+ breast cancer, including previously unreported signatures. While ER, stroma and proliferation-related signatures were associated with early prognosis, proliferation best predicted worse DFS after 5 yrs. NGS of the primary tumor is most informative for early events in pts with only 5 years of T, with few genes selecting only for late relapse. If validated, these signatures may identify pts with excellent DFS despite positive nodes for endocrine therapy alone as well as others for whom chemotherapy and/or biologics are also required
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SUPPORT: NCI CA 180888, 180819, 180821, 180820, 180863; in part, Genomic Health, Inc.

Thursday, December 10, 2015 9:45 AM

Oral Session: General Session 3 (9:30 AM-11:30 AM)