

Discovery of molecular predictors of late breast cancer specific events (BCSE) in ER+, node+ breast cancer – new transcriptome expression whole gene analysis of the phase III adjuvant trial SWOG S8814

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BACKGROUND: Unique genes and pathways were identified for prognosis on tamoxifen (T, 5 yrs) and prediction on CAF-T vs T in S8814 using whole transcriptome RNA-Seq from archival FFPE tissue. (Albain, et al; Cherbavaz, et al; SABCS 2015) Discovery was robust for early DFS events but sparse for late. The aims of this new analysis were to 1) utilize a new endpoint BCSE for gene discovery of late events, prognosis and prediction and 2) add intronic counts to the previous exonic results to define whole genes impacting on late BCSE.

METHODS: Charts of patients (pts) on CAF-T (212) vs T (142) were reviewed to define the BCSE endpoint (local/regional, contralateral, distant). Deaths without BC were treated as competing risks. BCSE models (including metagenes) of late prognosis and prediction used cumulative incidence functions. Consolidated intronic regions counts within genes were added to exonic regions counts. Using these “whole gene” (WG) counts, association of gene expression with time to BCSE was assessed by Cox regression. A multiple WG score (MWGS) for BCSE prognosis beyond 5 yrs (to 12.5 yrs) was constructed and evaluated for 1-3 and 4+ node (N) groups. False discovery rate was controlled at 10%.

RESULTS: More exons and WG were discovered for prognosis on T alone over 12.5 yrs with the BCSE endpoint than DFS. For prognosis of late BCSE after 5 yrs, more genes were discovered using WG (n=111) than by exons (n=9). There were significantly fewer genes for late BCSE on CAF-T (8, WG; 0, exons). The functions of WG prognostic for late BCSE were: cell cycle/proliferation-26 genes, chromosome segregation/mitotic spindle-22, DNA repair/maintenance-10, transcriptional/translational control-5, cell adhesion/migration-4, immune-3, diverse/unknown-32 and growth factor/hormone receptor signaling-9 (this group was only found by WGs, not exons). Of these 111 WG, a MWGS prognostic for late BCSE on T used 57 previously discovered genes pre-specified for this analysis. Probability of BCSE beyond 5 yrs for low vs high MWGS was 8% vs 21% in N1-3+ and 17% vs 42% in N4+. Late prognosis on T differed by low vs high risk defined in a metagene model: cumulative BCSE at year 10 was 0% vs 47% (low vs high risk, p=0.001). Prediction of 10-yr incidence of BCSE varied by risk level by treatment in a metagene model: low risk- CAF-T=47%, T=0% (p=0.045); high risk- CAF-T=35%, T=45% (p=0.027).

CONCLUSIONS: Gene discovery for prognosis of late BCSE is enhanced with a novel WG transcriptome expression approach. Use of chemotherapy (CT) before T significantly attenuated gene discovery, so that molecular tools for decisions on extending endocrine therapy (ET) may not be reliable in a setting of prior CT. Some pts on ET for 5 yrs may not require either longer ET or CT, given a N+ cohort was defined with no BCSE observed over 12.5 yrs. For prediction of CT benefit, CAF-T appeared to be inferior to T in a low risk metagene model for BCSE. In sum, these results add more evidence that ET alone may be sufficient (perhaps better) in select N+ settings. Validation in SWOG S1007 (RxPONDER) is planned.

SUPPORT: NCI CA180888, 180819, 180821, 180820, 180863; in part, Genomic Health, Inc.

Session: Poster Discussion: Multi Gene Markers and Decision Making (7:30 AM-9:00 AM)

Date/Time: Friday, December 9, 2016 - 7:30 am

Room: Stars at Night Ballroom 1&2 - 3rd Level

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