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Prediction of 10-Year Chemotherapy Benefit and Breast Cancer-Specific Survival by the 21-Gene Recurrence Score (RS) Assay in Node-Positive, ER-Positive Breast Cancer – An Update of SWOG-8814 (INT0100).

Author: Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh I-T, Ravdin P, Bugarini R, Baehner FL, Davidson NE, Sledge GW, Winer EP, Hudis C, Ingle JN, Perez EA, Pritchard KI, Shepherd L, Gralow JR, Yoshizawa C, Allred DC, Osborne CK, Hayes DF, For The Breast Cancer Intergroup of North America Loyola University Chicago Cardinal Bernardin Cancer Center, Maywood, IL

Background: A low 21-gene RS identifies patients with ER-positive breast cancer who do not appear to benefit from anthracycline-based chemotherapy (CAF) added to tamoxifen (T) despite positive axillary lymph nodes (Albain KS, et al. *Lancet Oncology*, In Press). However, in the low RS group, the lack of improvement by CAF in the 64% disease-free survival (DFS) at 10 years is not considered definitive evidence against the use of chemotherapy for conventionally-identified high risk patients. We conducted new DFS prediction analyses within nodal categories by RS over 10 years and assessed whether the assay has predictive utility for breast cancer specific survival (BCSS).

Methods: RT-PCR analyses for the 21 gene RS assay were feasible in 148 patients on T from the parent trial treated and 219 on CAF followed by T, as previously described. In this update, we conducted 10-year DFS analyses within nodal categories 1-3+ and 4+ by the linear RS. For the exploratory analysis of BCSS, only deaths due to breast cancer were counted as events, censoring deaths due to other causes (such as late cardiovascular events) as well as patients alive at the last follow-up visit. The clinically-utilized (trichotomized) RS categories of low (<18), intermediate (18-30) and high (≥ 31) were used for the BCSS analysis, and log-rank p-values were stratified by nodes.

Results: As with the previously reported 5-year DFS analysis by nodal status and linear RS, there was no apparent DFS benefit to CAF in the lower Recurrence Scores over 10 years for either the 1-3+ or 4+ nodal groups. Specifically (for both nodal groups), the 10-year DFS treatment curves overlapped for scores 0-10 and then started diverging at about RS=11, though any clinically meaningful CAF benefit for DFS was not evident until much higher Recurrence Scores. There was no BCSS benefit from CAF in either the low RS (log-rank p=0.56) or intermediate RS (log-rank p=0.89) categories, but CAF resulted in superior BCSS in the high RS category (log-rank p=0.033). The 10-year estimates for BCSS for low RS were 92% (95% CI 79%-97%) for T and 87% (95% CI 76%-93%) for CAF-T. In the intermediate RS, 10-year BCSS estimates were 70% (50%-83%) for T and 81% (67%-89%) for CAF-T; and in the high RS, 10-year BCSS estimates were 54% (38%-68%) for T and 73% (60%-82%) for CAF-T.

Conclusions: These additional exploratory analyses reinforce our initial interpretation that anthracycline-based chemotherapy does not appear to benefit patients with either 1-3 or 4 or more positive nodes over 10 years, if their tumors have a low RS. A prospective

study to confirm and extend these results has been proposed. New adjuvant treatment strategies for tumors with this distinct biology should be a high research priority.

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