

Oncotype DX Breast Recurrence Score[®] Report

Important Update on the RxPONDER Trial Results in Node Positive Breast Cancer

The SWOG S1007 study, known as RxPONDER, is a prospective multinational phase III clinical trial in women (≥18yrs) with hormone receptor-positive, HER2-negative invasive breast cancer with 1-3 positive axillary lymph nodes. 5015 eligible women with a Recurrence Score[®] result of 0-25 were randomized to endocrine therapy (ET) alone versus chemotherapy (CT) followed by endocrine therapy. Women with a Recurrence Score result of 26-100 were all recommended for chemotherapy followed by endocrine therapy¹.

The first results of RxPONDER were presented at the San Antonio Breast Cancer Symposium in December 2020². Median follow-up at this analysis was 5.1 years.

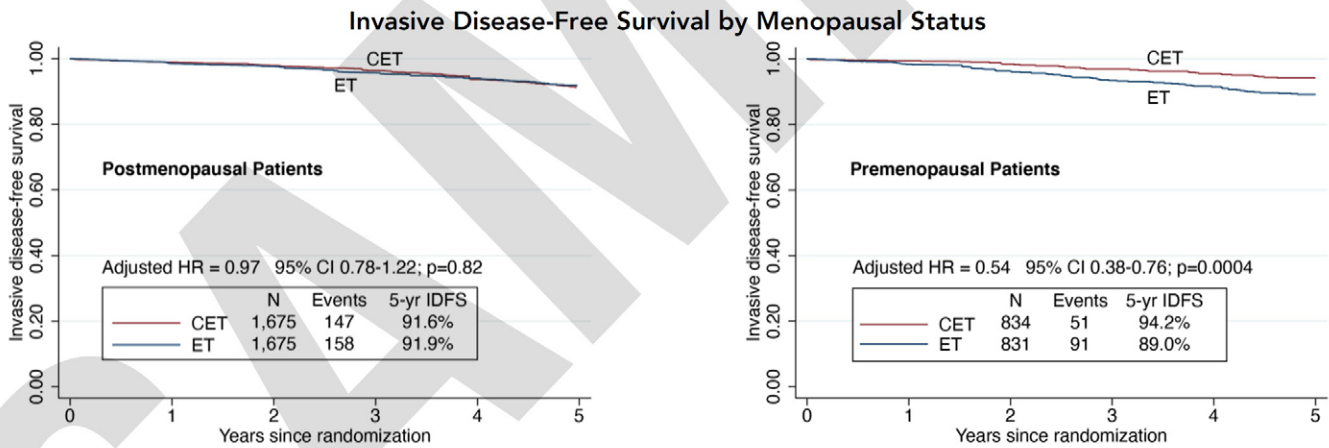
RxPONDER Results by Menopausal Status³ – Effect of chemotherapy on invasive disease-free survival⁴ (IDFS) in 5015 women with 1-3 positive axillary lymph nodes and RS 0-25.

Postmenopausal women with RS 0-25 did not show benefit in IDFS from the addition of chemotherapy to endocrine therapy (adjusted HR = 0.97, 95% CI 0.78-1.22, p=0.82).

Consistent lack of chemotherapy benefit was observed for subgroups of age, tumor size, grade, Recurrence Score result, and number of positive nodes. Overall, the absolute difference in distant recurrence rates at 5 years with chemotherapy was 0.3%.

Premenopausal women with RS 0-25 had a significant benefit in IDFS from the addition of chemotherapy to endocrine therapy (adjusted HR 0.54, 95% CI 0.38-0.76, p=0.0004).

Consistent benefit of chemotherapy was observed for subgroups of age, tumor size, Recurrence Score result, and number of positive nodes. Overall, the absolute difference in distant recurrence rates at 5 years with chemotherapy was 2.9%.



References:

1. Albain et al, *Lancet Oncology* 2009.
2. Kalinsky et al, *San Antonio Breast Cancer Symposium* 2020.
3. Definition of Menopausal Status:
 Premenopausal: Less than 6 months since last menstrual period and not on estrogen replacement.
 Postmenopausal: More than 12 months since last menstrual period with no prior hysterectomy OR prior bilateral oophorectomy.
 If the above categories are not applicable: <50 years is premenopausal, ≥50 years is postmenopausal.
4. Definition of Invasive Disease-Free Survival (IDFS):
 Invasive recurrence (local, regional, or distant), second invasive primary cancer (breast or not), death due to any cause.

Laboratory Director(s): William P. Joseph, M.D.

Genomic Health, Inc., 301 Penobscot Drive, Redwood City, CA 94063, USA - CLIA Number 05D1018272

This test was developed and its performance characteristics determined by Genomic Health, Inc. It has not been cleared or approved by the FDA, nor is it currently required to be. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research.

Oncotype DX Breast Recurrence Score[®] Report

Micromets & Node Positive (1-3)

IBC_45_HOHL1_PTLN1PT, IBC_45_HOHL1_PTFN1PT MN1

Date of Birth: 01-Feb-1950 Gender: Female Report Number: OR001294462-01 Report Date: 03-Feb-2021

Specimen Source/ID: Breast/ESI_OR001294462_Ab1

Ordering Physician: IBC_45_hohl1_hpsyfn1_001 mn1, IBC_45_hohl1_hpsyln1_001

<p>Recurrence Score[®] (RS) Result</p> <hr/> <div style="text-align: center; font-size: 48pt; font-weight: bold; color: orange;">24</div>	<p>Distant Recurrence Risk at 9 Years</p> <hr/> <p>With AI or TAM Alone</p> <div style="text-align: center; font-size: 48pt; font-weight: bold;">19%</div> <p>95% CI (14%, 24%)</p> <p>TransATAC</p>	<p>Group Average Absolute Chemotherapy (CT) Benefit*</p> <hr/> <p>RS 18-30</p> <p style="text-align: center; font-weight: bold;">CT Benefit for this group cannot be excluded.</p> <p>95% CI (-5%, 7%)</p> <p>SWOG 8814</p>
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Clinical factors may be considered with the RS when making individual treatment decisions.

AI = Aromatase Inhibitor / TAM = Tamoxifen
CI = Confidence Intervals

*For estimated CT benefit for individual RS results, see page 2.

Real World Evidence of SEER Registry Outcomes in Patients Treated Without CT Based on RS Results

	RS 0-10	RS 11-15	RS 16-20	RS 21-25	RS 26-100
# of Patients	1808	2196	1754	692	364
BCSS at 9 Years	98.2%	99.0%	96.7%	93.1%	84.2%

BCSS = Breast cancer-specific survival

Quantitative Single-Gene Scores



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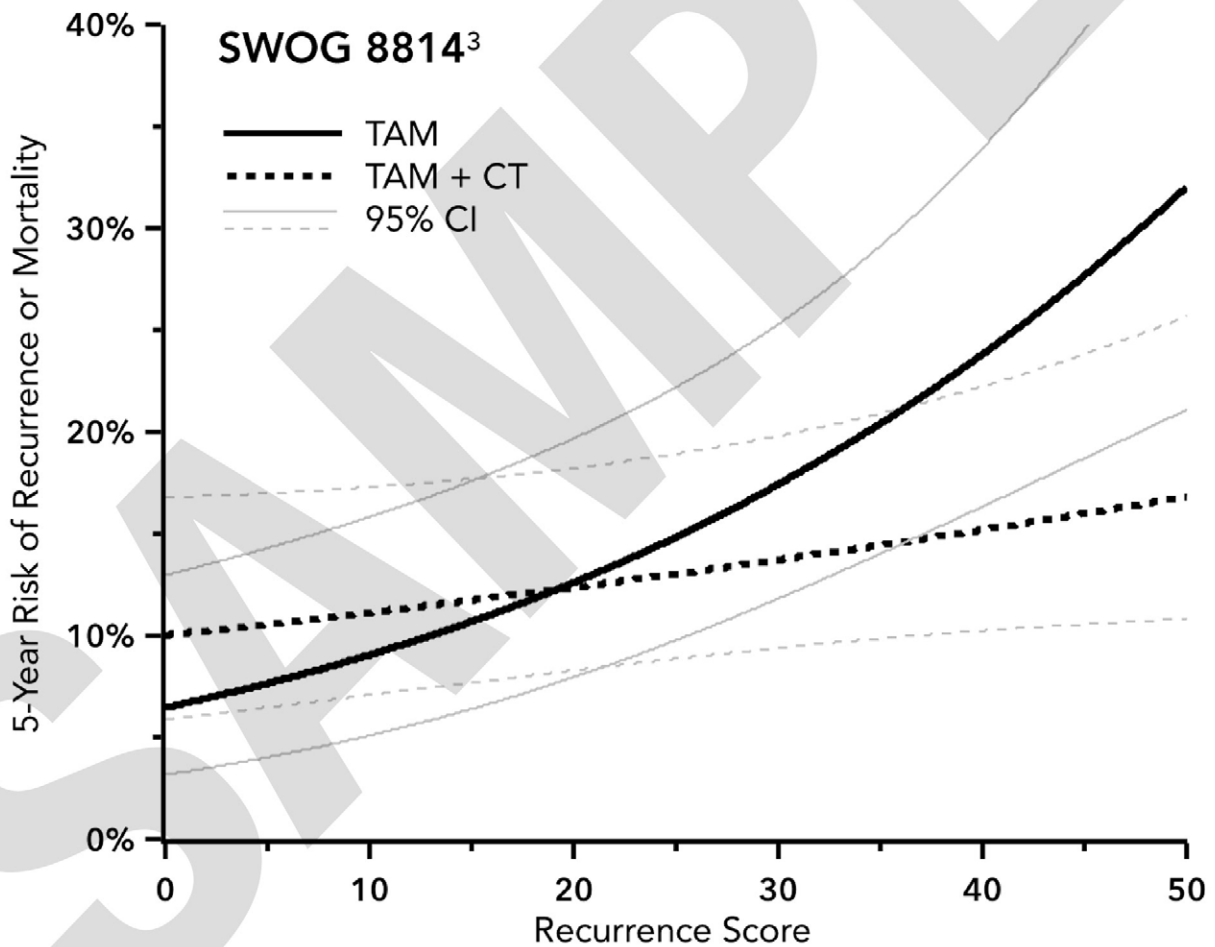
Report Number: OR001294462-01

Report Date: 03-Feb-2021

Specimen Source/ID: Breast/ESI_OR001294462_Ab1

Ordering Physician: IBC_45_hohl1_hpsyfn1_001 mn1, IBC_45_hohl1_hpsyln1_001

Estimated Chemotherapy Benefit for Individual Recurrence Score Results



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Date of Birth: 01-Feb-1950

Gender: Female

Report Number: OR001294462-01

Report Date: 03-Feb-2021

Specimen Source/ID: Breast/ESI_OR001294462_Ab1

Ordering Physician: IBC_45_hohl1_hpsyfn1_001 mn1, IBC_45_hohl1_hpsyln1_001

Medical Record/Patient #: MRN#_3Éĭ_1

Date of Collection: Unable to Obtain

Specimen Received: 03-Feb-2021

Additional Recipient: IBC_45_hohl1_hpsyfn_003 mn, IBC_45_hohl1_hpsyln_003

The Oncotype DX Breast Recurrence Score test uses RT-PCR to determine the expression of a panel of 21 genes (16 cancer-related, 5 reference) in tumor tissue.

The Oncotype DX Breast Recurrence Score test uses RT-PCR to provide prognostic and predictive information to guide the systemic treatment decisions with hormonal therapy and/or chemotherapy for patients diagnosed with ER+, HER2- invasive breast cancer. Decisions on treatment should also be based on independent medical judgment of the treating physician taking into consideration all available information concerning the patient's medical condition, including other pathological tests, in accordance with your communities' standard of care.

Results in this report are based on studies including both micrometastases and 1-3 positive nodes.

Advances in histopathological techniques and changes in staging criteria have resulted in an increase in the number of patients diagnosed with lymph node micrometastases (0.2 mm - 2.0 mm). Previous study results varied regarding their clinical significance. BCSS in SEER¹ for patients with RS 0-17 treated without chemotherapy are similarly favorable for patients with negative nodes, micrometastases, and 1-3 positive nodes.

The **Recurrence Score (RS) Result**, which ranges from 0-100, is calculated from the quantitative RT-PCR analysis of the 21 genes.

The **Distant Recurrence Risk** at 9 Years (Prognosis), in patients treated with tamoxifen or arimidex alone, is provided by the TransATAC² trial. Risk is for individual RS results. The 95% confidence intervals for distant recurrence at 9 years are ± 3 to $\pm 6\%$ for RS 0-22, and range from ± 6 to $\pm 12\%$ as RS increases from RS 23-50. The TransATAC trial enrolled 1,231 patients and 243 patients had 1-3 positive nodes, including micrometastases.

The **Absolute Benefit of Chemotherapy** is provided by the SWOG 8814³ trial. Results for reduction in distant recurrence or death at 5 years are for the RS groups 0-17, 18-30, and 31-100. The SWOG 8814 trial enrolled 367 patients with N+ (including micrometastases), ER+ breast cancer who were randomized to tamoxifen alone or tamoxifen plus CAF (anthracycline-containing) chemotherapy. The benefit of chemotherapy increased with an increase in the RS result. The upper bound of the 95% confidence interval for RS 18-30 was 7% absolute chemotherapy benefit.

Real World Evidence of SEER Registry Outcomes in Patients Treated Without Chemotherapy Based on RS Results

SEER had 6,814 patients with HR+, HER2-, node positive (1-3 positive nodes or micrometastases) breast cancer, diagnosed between January 2004 and December 2014, who were reported to have no or unknown chemotherapy use. Two additional prospective studies also demonstrated favorable outcomes with endocrine therapy alone for patients with 1-3 positive nodes and RS 0-11 (PlanB⁴) or RS 0-17 (Clalit⁵).

Quantitative Single-Gene Scores for quality control. The Oncotype DX test uses quantitative RT-PCR to determine the RNA expression of ER, PR, and HER2, using the published validated cut-offs⁶. The standard deviations of single-gene results are less than 0.5 units. The RT-PCR single-gene results may differ from ER, PR, or HER2 results reported using other methods or reported by other laboratories.

References:

1. Roberts et al. *Breast Cancer Res Treat.* 2017.; Genomic Health (data on file).
2. Dowsett et al. *J Clin Oncol.* 2010.
3. Albain et al. *Lancet Oncol.* 2010.; Genomic Health (data on file).
4. Nitz et al. *Breast Cancer Res Treat.* 2017.
5. Stemmer et al. *npj Breast Cancer* 2017.
6. Badve et al. *J Clin Oncol.* 2008.; Baehner et al. *J Clin Oncol.* 2010.