A novel DCIS biosignature identifies two subsets of women with HER2(+) DCIS with significantly different risks of local recurrence after BCS and RT

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Background

- NASBP-B43 was designed to determine if two doses of trastuzumab would improve local control after breast-conserving surgery (BCS) plus radiation therapy (RT) in women with HER2(+) breast ductal carcinoma in situ (DCIS).
- The trial demonstrated a non-statistically significant advantage to the drug in reducing ipsilateral breast tumor recurrence (IBTR).
- The DCIS biosignature (PreludeDxTM, Laguna Hills, CA) has been shown to be prognostic of 10-year IBR risk and predictive of RT benefit.
- Nevertheless, our data revealed that there remains a subpopulation of patients with an elevated risk of recurrence despite BCS and RT.
- We therefore developed a novel Residual Risk subtype (RRt) biosignature that identifies a subset of patients within HER2(+) DCIS with a much higher recurrence risk after BCS plus RT.
- In this study, we analyzed a cohort of women with HER2(+) DCIS treated with BCS plus RT to determine if the biosignature could identify subsets of women with a) higher recurrence risk after BCS plus RT who may benefit from further therapy, such as trastuzumab and b) low risk after BCS plus RT who would not likely benefit from further therapy to reduce local recurrence.

Methods

- DCISionRT with the integrated residual risk biosignature (DCISionRT + RRt) was evaluated on a subset of 178 women with HER2(+) DCIS who were treated with BCS and RT in a multinational cohort of 926 patients from the United States of America, Sweden, and Australia who were used in the validation studies for DCISionRT.
- Central pathology review and biosignature testing were performed at a CLIA-certified lab (Laguna Hills, CA). HER2(+) DCIS was defined as patients with a HER2 3+ immunohistochemistry ≥10% (ASCO/CAP).
- The biosignature identified patients with and without Residual Risk (RR). Individual patient outcome and biosignature results were analyzed independently (McCloud Consulting).

Results

- The biosignature classified 113 of 178 HER2(+) women (63%) into the Residual Risk group (DS>2.8 with RRt).
- Patients were similarly classified as RR independent of age or tumor size (Table 1).
- Grade 3 was more common in the RR group than the no RR (87% vs. 63%) group.
- In the RT-treated patients, those with RR had a significantly higher 10-year total IBR rate of 16.2% (95%CI 9.7%-26.5%) than the patients without RR 1.6% (95%CI 0.2%-10.9%) (p=0.012).
- Similar results were observed for invasive recurrence.

- DCISionRT with Residual Risk Subtype identified two thirds of patients with HER2 (3+) who had significantly higher Residual Risk after RT
- Patients with the Residual Risk Subtype may benefit from further therapy, such as HER2-directed therapies

Table 1. HER2(+) DCIS Patients Treated with RT with or w/o Concurrent Trastuzumab in NASBP-B43 Trial

	RT	RT plus Trastuzumab	HR 95% CI p-value
IBTR	6.3%	5.0%	0.81 (0.56 - 1.17) p = 0.26
Annual Rate of IBTR	0.99%	0.79%	

Figure 1. 10-Year IBR Risk in RT-treated HER2(+) DCIS patients by Biosignature Risk Groups

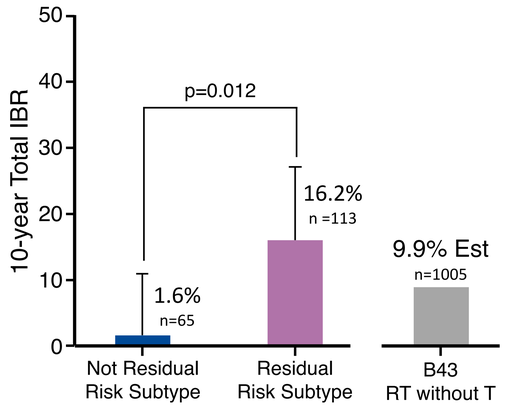
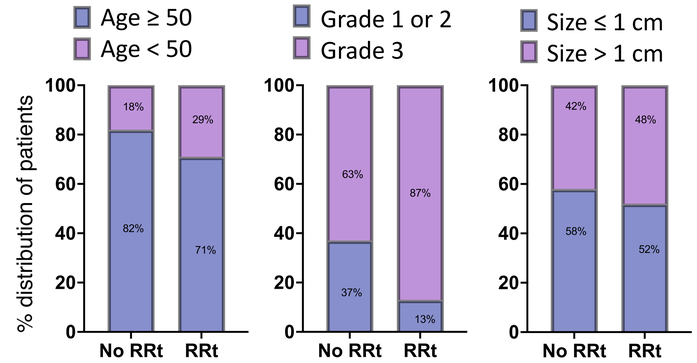


Table 2. Clinicopathological feature distribution by biosignature risk groups

	HER2(+) not RRt n (%)	HER2(+) RRt n (%)	All HER2(+) Patients	p-value
All Patients	65 (37)	113 (63)	178 (100)	
Age <50	12 (18)	33 (29)	45 (25)	0.15
Age ≥50	53 (82)	80 (71)	133 (75)	
Nuclear Grade 1 or 2	24 (37)	15 (13)	39 (22)	<0.001
Nuclear Grade 3	41 (63)	98 (87)	139 (78)	
Size ≤ 1 cm	38 (58)	59 (52)	97 (54)	0.44
Size > 1 cm	27 (42)	54 (48)	81 (46)	

Figure 2. Clinicopathological feature distribution by biosignature risk groups



Conclusions

- The new, integrated biosignature was predictive for 10-year IBR risk after BCS plus RT in women with HER2(+) DCIS.
- The biosignature identified 1) a subtype of women with a HER2(+) DCIS with suboptimal benefit to adjuvant RT (63%) who had significantly elevated 10-year IBR risk remaining after BCS and RT compared to those without RR who had low 10-year IBR risk after BCS and RT.
- Collectively, this suggests that there is a subpopulation of HER2(+) DCIS that may benefit from further therapy, such as HER2-directed therapies.