All HER2-Positive Tumors are not Created Equal

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Tumor biologic features, including hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status, have predictive and prognostic value in breast cancer patients. For this reason, in addition to providing information regarding histology and grade, pathology reports routinely report the status of the HRs, including the estrogen and progesterone receptors, as assessed by immunohistochemistry (IHC), as well as HER2 status assessed by IHC, and, in some cases, in situ hybridization techniques.^{1,2} Treatment recommendations are then made based largely on HR and HER2 expression, with patients with HR-positive (HR+) tumors receiving endocrine therapy and patients with HER2-positive (HER2+) tumors receiving HER2-targeted therapy.^{3–6}

In addition to assessing HR and HER2 status, there is growing interest in further interrogating tumor biology using gene expression array analyses in order to personalize therapy. Two reports from prospective clinical trials have provided high-level evidence for clinical use of these assays. An initial report from the Trial Assigning Individualized Options for Treatment (TAILORx) study that evaluated the use of the 21-gene Oncotype DX recurrence score in patients with HR+, HER2– lymph node-negative breast cancer, showed that patients with tumors having a recurrence score <11 had low-risk biology and required endocrine therapy alone.⁷ After a median follow-up of almost 6 years, these patients had recurrence-free survival and overall survival rates of 99 and 98%, respectively. More recently, data were published from the MINDACT

study, a prospective randomized trial that utilized MammaPrint, a 70-gene signature, to evaluate the impact of chemotherapy on patients identified to be at high risk for metastases based on clinical factors, but low genomic risk based on their MammaPrint results.⁸ The study showed that patients at low genomic risk who did not receive chemotherapy had 5-year distant metastasis-free survival rates (94.4%) that were similar to those of patients receiving chemotherapy (95.9%). Approximately 80% of patients in the MINDACT trial had node-negative disease, 81% had HR+/HER2– tumors, and approximately 10% had HER2+ tumors. Taken together, the results of these studies support investigating the use of genomic assays to identify low-risk biology that will allow personalization of treatment recommendations. Current National Comprehensive Cancer Network and American Society of Clinical Oncology (ASCO) guidelines limit their recommendation for use of Oncotype and Mammamprint to patients with HR+/HER2– tumors.^{3,9}

Efforts to personalize treatment recommendations are dependent on being able to determine if the factors used for personalization, to include subtypes as determined by IHC or molecular subtypes determined by multigene assays, predict response to therapy. Administering treatment in the neoadjuvant setting provides that opportunity. The article accompanying this editorial is one of a series of reports from the Neoadjuvant Breast Registry Symphony Trial (NBRST) that sought to compare chemosensitivity, as defined by pathologic complete response (pCR) rates, using the Blueprint functional subtype profile versus conventional IHC/fluorescent in situ hybridization (FISH) subtyping.^{10–12} The NBRST represents a ‘real world’ study in that patients were not administered protocol-prescribed treatment, rather they received chemotherapy at the discretion of their physician using any of a number of guideline-concordant regimens. The Blueprint molecular

subtyping profile is an 80-gene test developed from an initial cohort of 200 patients and validated on 784 samples from four independent cohorts. Based on molecular pathways, Blueprint identifies 'functional' subtypes, including luminal type, HER2 type, and basal type.¹³

The current article looks specifically at HER2+ patients enrolled in the NBRST.¹⁴ Since enrollment occurred between 2011 and 2014, it spans the time period during which pertuzumab was added to neoadjuvant regimens for HER2+ patients, providing a unique opportunity to investigate whether molecular subtyping can be used to determine which patients benefit from dual HER2-targeting. An important aspect of the study is that all 297 patients included in these analyses had HER2+ breast cancer as determined by their local institutions, presumably using standard guidelines from the ASCO and the College of American Pathologists (CAP). Among the 297 patients, 184 had HR+/HER2+ tumors, while 113 had HR-/HER2+ tumors. The pCR rates for these two groups among the patients treated with chemotherapy plus trastuzumab were 30% for HR+/HER2+ ($n = 111$) disease and 58% for HR-/HER2+ ($n = 67$) disease. This is consistent with data published in a pooled analysis of neoadjuvant chemotherapy trials from Cortazar et al. that was conducted to establish the association between pCR and survival. That analysis, which included almost 700 patients with HER2+ disease treated on studies evaluating trastuzumab, reported a pCR rate of 31% for patients with HR+/HER2+ disease versus 50% for patients with HR-/HER2+ disease.¹⁵ In the current study from Beitsch et al., as expected the pCR rates increased with the addition of pertuzumab, to 48% in patients with HR+/HER2+ ($n = 73$) tumors and 72% in those with HR-/HER2+ ($n = 46$) tumors.¹⁴ This is generally consistent with previously published data from the NeoSphere trial that looked at the addition of pertuzumab to trastuzumab and docetaxel.¹⁶ In that study, patients with HR+/HER2+ tumors randomized to the study arm receiving chemotherapy and dual HER2-targeted therapy had a pCR rate of 26%, compared with 63% in patients with HR-/HER2+ disease. It is possible that the difference in pCR rates between the NBRST and NeoSphere studies is due to differences in classification of HR status. The NBRST classified tumors as HR+, with as low as 1% positivity on IHC staining. The paper detailing the NeoSphere trial did not specifically state the cut-off used, but the study was conducted between 2007 and 2009, a time period during which ASCO guidelines used a 10% cut-off for HR+ classification. Data from the KRISTINE study, which included a cohort that received trastuzumab and pertuzumab in addition to taxotere and carboplatin (TCHP), were presented at the 2016 ASCO annual meeting. In that study, pCR rates were 44% in patients with HR+/HER2+

tumors and 73% in HR-/HER2+ tumors, very similar to the NBRST.⁹ Table 1 summarizes pCR rates from the various studies evaluating HER2-targeted regimens.

The NBRST investigators went on to classify HER2+ patients according to Blueprint subtype.¹⁴ For patients who were HR+/HER2+, the Blueprint subtype was luminal in 48%, HER2 in 44%, and basal in 8%. The pCR rates for luminal and HER2 types were 20 and 57%, respectively; there were too few patients in the basal type to report. For patients who were HR-/HER2+, the Blueprint subtype was luminal in 3%, HER2 in 71%, and basal in 27%. The pCR rates were 73% for the HER2 type and 40% for the basal type; there were too few patients in the luminal group to report. It is interesting to note that the pCR rates in the HER2 type by Blueprint still vary by HR status, i.e. 57% if HR+ versus 73% if HR-. This speaks to the complexity of the interaction between HR and HER2 biology.

The most striking finding in the current study came from the analyses of pCR rates by Blueprint subtype when comparing patients who received chemotherapy plus trastuzumab versus that same regimen with pertuzumab added (Table 2). Surprisingly, the addition of pertuzumab seemed to be most critical in patients classified as having luminal-type tumors. With trastuzumab alone, the pCR rate was 8%, which was increased to 31% with the addition of pertuzumab. It is an interesting observation that it was patients with the luminal-type tumors that appeared to benefit most from dual HER2-targeted therapy. This is in contrast to a report of the CALGB 40601 trial that investigated dual HER2-targeted therapy with trastuzumab and lapatinib in the neoadjuvant setting.¹⁷ In that study, patients receiving paclitaxel plus trastuzumab had a pCR rate of 41% if HR+/HER2+ versus 58% if HR-/HER2+. When lapatinib was added to the regimen, the pCR rate remained at 41% for HR+/HER2+, but was 79% for HR-/HER2+ patients. The effect of dual therapy was therefore only seen in patients with HR- disease. Why the difference? A recent analyses of biomarkers from the NeoSphere trial may provide insight.¹⁸ In that study, there were significant differences in biomarker expression in HR+ versus HR- tumors. Among these differences, HER3 messenger RNA (mRNA) expression and HER3 protein expression were higher in HR+ tumors. Given that one mechanism of action of pertuzumab, which binds to the extracellular domain II of HER2, is to inhibit ligand-dependent HER2/HER3 dimerization, one might hypothesize that this provides rationale for the dramatic difference in pCR rates with the addition of pertuzumab in patients who, per ASCO/CAP guidelines, were HER2+, but by Blueprint assay were categorized as luminal type. However, referring back to the NeoSphere study, the pCR rate for HR+/HER2+ patients receiving docetaxel plus trastuzumab was 20%, which increased to 26% with the addition of

TABLE 1 Pathologic complete response rates reported in select trials evaluating neoadjuvant therapy regimens incorporating HER2-targeted therapy

Regimen	Trial	pCR rate for HR+/HER2– (%)	pCR rate for HR–/HER2+ (%)
Chemotherapy + trastuzumab	NBRST ¹⁴	30	58
	NeoSphere ¹⁶	20	37
	CALGB 40601 ¹⁷	41	58
	Meta-analysis ¹⁵	31	50
Chemotherapy + trastuzumab + pertuzumab	NBRST ¹⁴	48	72
	NeoSphere ¹⁶	26	63
	KRISTINE ⁹	44	73
Chemotherapy + trastuzumab + lapatinib	CALGB 40601 ¹⁷	41	79

HER2 human epidermal growth factor receptor 2, pCR pathological complete response, HR hormone receptor, NBRST Neoadjuvant Breast Registry Symphony Trial, CALGB Cancer and Leukemia Group B

TABLE 2 Pathologic complete response rates by Blueprint subtype

Blueprint subtype	Chemotherapy + trastuzumab		Chemotherapy + trastuzumab + pertuzumab		p value
	N	pCR rate (%)	N	pCR rate (%)	
Luminal type	52	8	39	31	0.0055
HER2 type	95	57	66	76	0.0187
Basal type	31	45	14	43	1.000

pCR pathological complete response, HER2 human epidermal growth factor receptor 2

pertuzumab, a modest increase. In patients with HR–/HER2+ tumors, the pCR rate was 37% for those receiving docetaxel plus trastuzumab, which increased to 63% with the addition of pertuzumab. Clearly, the biology is complex.

While the data reported by Beitsch and colleagues are thought-provoking, it is important to note that the numbers of patients for each analysis is small. In addition, it is presumed that these were not prespecified subset analyses and the study was not powered to address this question. Like many biomarker studies, the findings are hypothesis-generating and warrant further evaluation. It is possible that some patients benefit more from the addition of pertuzumab, and it is clear that biomarkers of response are greatly needed. However, today, patients with HER2+ tumors treated with neoadjuvant systemic chemotherapy should be offered the best available therapy, which includes trastuzumab and pertuzumab-based chemotherapy.

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