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# Seven-Year Follow-Up Analysis of Adjuvant Paclitaxel and Trastuzumab Trial for Node-Negative, Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer

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## abstract

**PURPOSE** The Adjuvant Paclitaxel and Trastuzumab trial was designed to address treatment of patients with small human epidermal growth factor receptor 2 (HER2)–positive breast cancer. The primary analysis of the Adjuvant Paclitaxel and Trastuzumab trial demonstrated a 3-year disease-free survival (DFS) of 98.7%. In this planned secondary analysis, we report longer-term outcomes and exploratory results to characterize the biology of small HER2-positive tumors and genetic factors that may predispose to paclitaxel-induced peripheral neuropathy (TIPN).

**PATIENTS AND METHODS** In this phase II study, patients with HER2-positive breast cancer with tumors 3 cm or smaller and negative nodes received paclitaxel (80 mg/m<sup>2</sup>) with trastuzumab for 12 weeks, followed by trastuzumab for 9 months. The primary end point was DFS. Recurrence-free interval (RFI), breast cancer–specific survival, and overall survival (OS) were also analyzed. In an exploratory analysis, intrinsic subtyping by PAM50 (Prosigna) and calculation of the risk of recurrence score were performed on the nCounter analysis system on archival tissue. Genotyping was performed to investigate TIPN.

**RESULTS** A total of 410 patients were enrolled from October 2007 to September 2010. After a median follow-up of 6.5 years, there were 23 DFS events. The 7-year DFS was 93% (95% CI, 90.4 to 96.2) with four (1.0%) distant recurrences, 7-year OS was 95% (95% CI, 92.4 to 97.7), and 7-year RFI was 97.5% (95% CI, 95.9 to 99.1). PAM50 analyses (n = 278) showed that most tumors were HER2-enriched (66%), followed by luminal B (14%), luminal A (13%), and basal-like (8%). Genotyping (n = 230) identified one single-nucleotide polymorphism, *rs3012437*, associated with an increased risk of TIPN in patients with grade 2 or greater TIPN (10.4%).

**CONCLUSION** With longer follow-up, adjuvant paclitaxel and trastuzumab is associated with excellent long-term outcomes. Distribution of PAM50 intrinsic subtypes in small HER2-positive tumors is similar to that previously reported for larger tumors.

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## INTRODUCTION

Longer-term follow-up of the large pivotal trials has confirmed a dramatic and sustained benefit of the addition of trastuzumab to standard adjuvant chemotherapy in patients with early-stage, human epidermal growth factor receptor 2 (HER2)–positive breast cancer, reducing both the risk of recurrence and death.<sup>1-3</sup> Moreover, the benefits of trastuzumab are independent of age, tumor size, nodal status, and hormone receptor (HR) status.

Retrospective data suggest that patients with small, node-negative HER2-positive tumors have recurrence rates that range from 5% to 30%.<sup>4,5</sup> However, randomized trials of adjuvant trastuzumab included

a limited number of patients with stage I disease. To our knowledge, the Adjuvant Paclitaxel and Trastuzumab (APT) trial<sup>6</sup> was the first study designed to specifically address the appropriate treatment approach for patients with small, node-negative HER2-positive breast cancer. This study was a single-arm trial, because it was believed that a randomized study would not be feasible given retrospective data suggesting more than a minimal risk of recurrence for this population. Furthermore, there was no standard treatment at that time for patients with small node-negative HER2-positive tumors to define a control arm. The first report of the APT trial in 2015 after a median follow-up of 4 years showed a 3-year rate of survival

## ASSOCIATED CONTENT

### Appendix

### Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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free from invasive disease of 98.7% (95% CI, 97.6 to 99.8) and a low rate of serious adverse events.<sup>6</sup> Because the majority of patients included in this trial had HR-positive, HER2-positive breast cancers, which are believed to be associated with later recurrences,<sup>1,2</sup> long-term follow-up of this trial was important to better determine the true efficacy of this regimen.

In addition, HER2-positive breast cancer is a biologically heterogeneous disease,<sup>7</sup> with different treatment sensitivities and survival outcomes. Work looking at larger HER2-positive breast cancers has shown that all four intrinsic molecular subtypes can be identified by gene expression analyses.<sup>8</sup> However, molecular profiling of small HER2-positive tumors is largely unknown, and we sought to better characterize these small, node-negative tumors.

In this planned secondary analysis of the APT trial, we report the updated results on 7-year disease-free survival (DFS), recurrence-free interval (RFI), breast cancer-specific survival (BCSS), and overall survival (OS). We also report some exploratory analyses that include PAM50 intrinsic subtyping and risk of recurrence (ROR) score performed on the available archival tissue, to better characterize this patient population with small, node-negative HER2-positive disease, because it may provide deeper insights into potential therapeutic approaches. We also evaluated genotyping for the association of genetic variants and paclitaxel-induced peripheral neuropathy (TIPN), given that this is one of the most burdensome long-term effects of paclitaxel-containing regimens, and efforts to predict and prevent such toxicity are warranted.

## PATIENTS AND METHODS

### Study Design and Patient Population

The APT study was a multicenter, single-arm, investigator-initiated phase II trial. Details of the study design and study population have been previously reported.<sup>6</sup> Eligible patients had HER2-positive breast cancer, pathologically confirmed by local testing either through immunohistochemistry 3+ intensity or amplification of the HER2 gene on fluorescence in situ hybridization 2.0 or greater. Primary invasive tumor had to measure 3.0 cm or smaller in the greatest dimension, and patients had to have node-negative disease (although the protocol was amended in June 2, 2009 after 188 patients enrolled to allow patients with a single micrometastatic node [Data Supplement]). The protocol required patients to have a left ventricular ejection fraction of at least 50% (by echocardiography or multiple-gated acquisition). Other requirements included no prior myocardial infarction or uncontrolled hypertension, no neuropathy higher than grade 1, no prior malignancy within the past 5 years, and no prior history of invasive breast cancer.

### Procedures

Adjuvant treatment consisted of weekly paclitaxel (80 mg/m<sup>2</sup>) plus weekly trastuzumab for 12 weeks followed by

single-agent trastuzumab every 3 weeks for a total of 13 doses. Genentech provided funding for the study, but paclitaxel and trastuzumab were commercially supplied. Adjuvant endocrine therapy was recommended as per institutional standard for women with HR-positive tumors after the completion of paclitaxel therapy. Adjuvant radiation therapy was also performed according to local institutional standards. Patients could be treated with conventional post-chemotherapy whole-breast radiation or partial breast radiation administered by external beam or brachytherapy.

All patients adhered to the same schedule of follow-up visits. Left ventricular ejection fraction by echocardiography or multitargeted acquisition scanning was required at baseline, 12 weeks, 6 months, and 1 year after the start of protocol treatment. Clinical assessments after finishing trastuzumab monotherapy were scheduled every 6 months for the first 4 years and then annually during years 5 to 10 after study enrollment or until the end point was reached. An appropriate screening of residual breast tissue performed at least yearly was required. The institutional review board at each participating institution approved the study, and written informed consent from all the trial participants was provided before the study entry. A second consent was obtained from patients for extended follow-up.

### Statistical Considerations

Details of the statistical design were published previously.<sup>6</sup> The primary end point was DFS, which is the time from study enrollment to the first of the following events that define a failure: locoregional ipsilateral recurrence, contralateral invasive breast cancer, distant recurrence, or death from any cause, as defined by the Standardized Efficacy Endpoints criteria.<sup>9</sup> Participants who were alive and free from recurrence were censored at the date of the last follow-up. For patients who did not consent for additional follow-up, their survival time was censored at their off-study dates. Exploratory survival end points included RFI, BCSS, and OS. RFI was defined as the time from study enrollment to the first documentation of disease recurrence, including invasive locoregional recurrence or distant recurrence, and death as a result of breast cancer. BCSS was defined as the time from study enrollment until death as a result of breast cancer. OS was the time from study enrollment until death as a result of any cause.

In our primary analysis, a Poisson test was used to evaluate the failure rate at 3 years against a null hypothesis of 9.2% using a one-sided type I error of 0.05. The planned sample size was 400 patients, with interim futility analyses after 225 and 800 patient-years of follow-up and a final analysis after 1,600 patient-years of follow-up. Under this design, the probability of rejecting the null was 0.95 if the true 3-year failure rate is 5%. In this update analysis, the Kaplan-Meier method was used in estimating the survival function for primary and exploratory end points, and point estimates are reported with two-sided 95% CIs.

## PAM50 Intrinsic Subtype Analysis and ROR Score Calculation

Hematoxylin and eosin–stained slides from formalin-fixed paraffin-embedded (FFPE) surgical specimens were examined to confirm the presence of invasive tumor and to determine the minimum surface area for scraping and tumor enrichment. Total RNA was isolated from 5- $\mu$ m-thick FFPE slides for each tumor specimen using the Qiagen FFPE kit for RNA isolation from FFPE tissue (Qiagen, Hilde, Germany) following the manufacturer's protocol. RNA was quantified using the NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific Waltham, MA). A minimum of 200 ng of total RNA was used to measure the expression of the PAM50 subtype predictor genes. PAM50 gene expression analysis was conducted on the nCounter gene expression platform (NanoString Technologies, Seattle, WA). Data were analyzed using the Prosigna algorithm (NanoString Technologies) to determine the intrinsic subtype calls (luminal A, luminal B, HER2-enriched, or basal-like) and to generate ROR scores by mapping data to a validated subtype-based risk model as previously described.<sup>10,11</sup> Quality assessment and normalization were performed in nSolver 4.0 from NanoString Technologies, as per the manufacturer's instructions.

## Genotyping and Statistical Analysis for the Association of Genetic Variants and TIPN

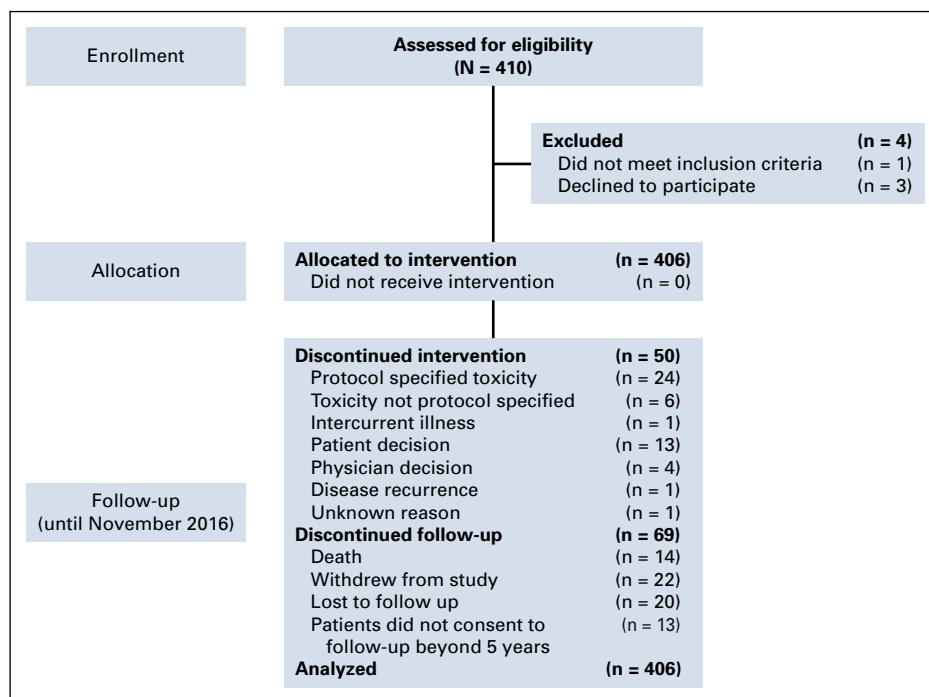
Top candidate germline single-nucleotide polymorphisms (SNPs) for TIPN were selected from prior correlative genome-wide analyses of TIPN in Eastern Cooperative Oncology Group trial E5103<sup>12</sup> and further evaluated here. All 51 candidate SNPs had a *P* value < .001 in the E5103

analysis, had linkage disequilibrium support, were from unique regions of the genome, and were confined to patients of European ancestry.<sup>12</sup> The SNPs were genotyped using blood DNA derived from APT trial with a QuantStudio 12K Flex OpenArray AccuFill System (Thermo Fisher Scientific) platform. SNPs were removed from the analysis if the call rate was less than 95%, minor allele frequency less than 3%, or the Hardy-Weinberg equilibrium *P* value < .001. A case-control analysis was performed for those of self-defined white race. Cases were defined as patients who received at least one dose of paclitaxel and experienced grade 2 or greater TIPN during treatment. Patients without TIPN served as controls. Logistic regression model was used in the statistical analysis. Age and body surface area were used as covariates, similar to our prior analyses.<sup>12</sup>

## RESULTS

Between October 9, 2007, and September 3, 2010, 410 patients were enrolled in the study and 406 started protocol therapy (Fig 1). Baseline patient characteristics are listed in Table 1. Overall, median age at enrollment was 55 years (range, 24 to 85 years), and most patients (67%) had HR-positive disease. Fifty percent of patients had tumors 1.0 cm or smaller, most of which were T1b. Only 9% of patients had tumors larger than 2 cm and up to 3 cm. Mean tumor size was 1.1 cm.

The results reported in our primary analysis published in 2015 included all data available as of April 21, 2014, with 1,605 patient-years of follow-up. The 3-year rate of DFS was 98.7% (95% CI, 97.6 to 99.8), with 12 DFS events reported (two distant recurrences). The long-term results reported here are from all data available as of November 11,



**FIG 1.** Trial enrollment and follow-up.

**TABLE 1.** Patient Baseline Characteristics From the Overall Cohort and From Patients With PAM50 Data

Characteristic	All Treated Patients (N = 406)	Patients With PAM50 Assessed (n = 278)	Patients Without PAM50 Assessed (n = 128)	P*
Age group, years				
< 50	132 (33)	79 (28)	53 (41)	.02
50-59	137 (34)	101 (36)	36 (28)	
60-69	96 (24)	64 (23)	32 (25)	
≥ 70	41 (10)	34 (12)	7 (5)	
Sex				
Female	405 (100)	277 (100)	128 (100)	1.00
Male	1 (< 1)	1 (< 1)	0 (0)	
Race				
White	351 (86)	242 (87)	109 (85)	.88
Black or African American	28 (7)	17 (6)	11 (9)	
Asian	11 (3)	8 (3)	3 (2)	
Other	16 (4)	11 (4)	5 (4)	
Size of primary tumor, cm				
T1mi (≤ 0.1)	9 (2)	1 (< 1)	8 (6)	< .001
T1a (0.1 to ≤ 0.5)	68 (17)	29 (10)	39 (30)	
T1b (> 0.5 to ≤ 1.0)	124 (31)	81 (29)	43 (34)	
T1c (> 1.0 to ≤ 2.0)	169 (42)	137 (49)	32 (25)	
T2 (> 2.0 to ≤ 3.0)	36 (9)	30 (11)	6 (5)	
Histologic grade				
I: Well differentiated	44 (11)	26 (9)	18 (14)	.02
II: Moderately differentiated	131 (32)	88 (32)	43 (34)	
III: Poorly differentiated	228 (56)	164 (59)	64 (50)	
Unknown	3 (1)	0 (0)	3 (2)	
ER status				
Positive	260 (64)	188 (68)	72 (56)	.03
Negative	141 (35)	88 (32)	53 (41)	
Borderline	5 (1)	2 (1)	3 (2)	
PR status				
Positive	201 (50)	150 (54)	51 (40)	.02
Negative	196 (48)	123 (44)	73 (57)	
Borderline	8 (2)	5 (2)	3 (2)	
Unknown	1 (< 1)	0 (0)	1 (1)	
HR status				
Positive	272 (67)	196 (70)	76 (59)	.03
Negative	134 (33)	82 (30)	52 (41)	

NOTE. Data given as No. (%).

Abbreviations: ER, estrogen receptor; HR, hormone receptor; PR, progesterone receptor.

\*P values were obtained using Fisher's exact test.

2016, which includes 2,390 patient-years of follow-up. After a median follow-up of 6.5 years (range, 0.02 to 8.9 years), there were 23 DFS events observed: five locoregional recurrences (1.2%), four distant recurrences (1%), six new contralateral breast cancers (1.5%), and eight deaths without

documented recurrence (2%; Table 2). The 7-year DFS was 93.3% (95% CI, 90.4 to 96.2) for the overall population (Fig 2); in patients with HR-positive tumors, the 7-year DFS was 94.6% (95% CI, 91.8 to 97.5), and among HR-negative patients, the 7-year DFS was 90.7% (95% CI, 84.6 to 97.2).

**TABLE 2.** DFS Events Observed

DFS Event	No. (%)	Time to Event (months), Median (range)
Any recurrence or death	23 (5.7)	
Local/regional recurrence	5 (1.2)	
Ipsilateral axilla (HER2 positive)	3	20 (12-54)
Ipsilateral breast (HER2 positive)	2	51 (37-65)
New contralateral primary breast cancer	6 (1.5)	
HER2 positive	1	56
HER2 negative	3	36 (12-59)
Unknown	2	87 (84-90)
Distant recurrence	4 (1.0)	53 (27-63)
Death		
Non-breast-cancer related	8 (2.0)	66 (13-71)

Abbreviations: DFS, disease-free survival; HER2, human epidermal growth factor receptor 2.

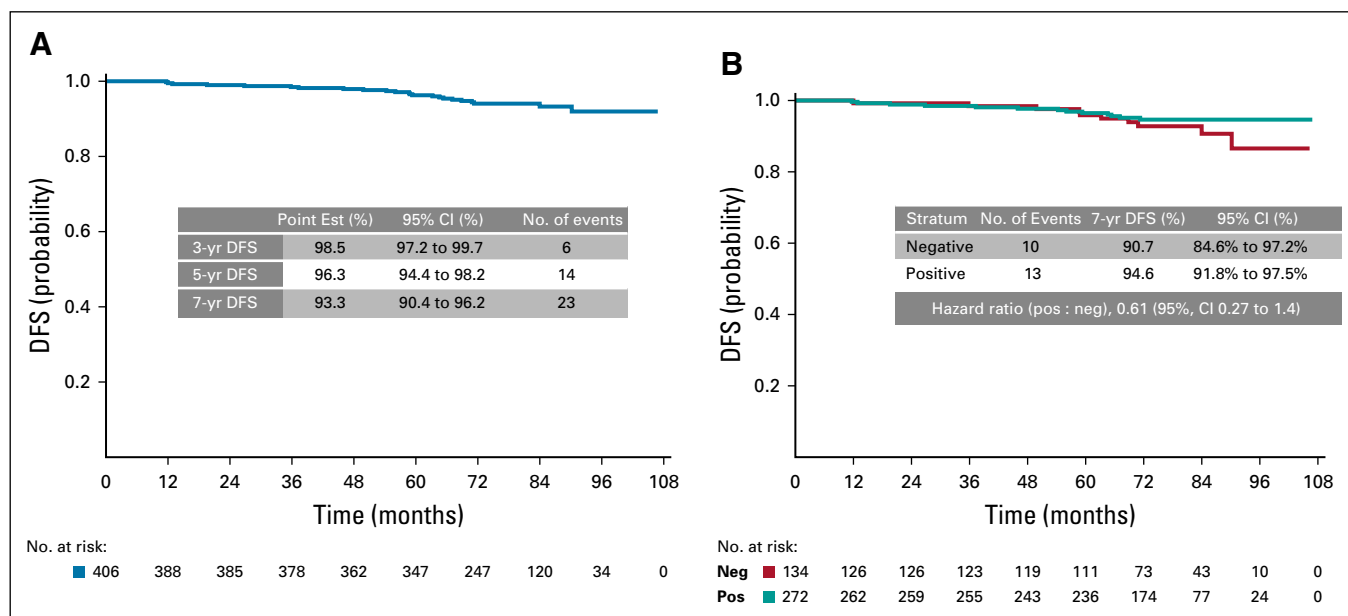
Seven-year RFI, which includes distant recurrence, death from breast cancer, and invasive locoregional recurrence, was 97.5% (95% CI, 95.9 to 99.1%). Seven-year BCSS was 98.6% (95% CI, 97.0 to 100%), and 7-year OS was 95.0% (95% CI, 92.4 to 97.7%; Table 3).

PAM50 gene expression profiling was successfully performed in 278 patients (Appendix Fig A1, online only). The overall cohort and the cohort of the subset of patients with PAM50 data presented similar baseline characteristics (Table 1), although there were significantly more patients with larger and poorly differentiated tumors in the cohort of PAM50 assessed than in the overall cohort. Distribution of PAM50 subtypes is listed in Table 4. The majority of tumors

were classified as HER2 enriched (65.5%), followed by luminal B (13.7%), luminal A (12.6%), and basal-like (7.9%). Subtype distribution differed significantly by HR status (Table 4). A greater percentage of HR-negative patients were HER2 enriched (84% v 58%,  $P < .001$ ) and basal-like (13% v 6%;  $P < .001$ ) than in the HR-positive cohort, and no cases of luminal B were found in HR-negative tumors. The low event rate observed prevents making statistical inferences on the prognostic value of molecular intrinsic subtypes. Appendix Table A1 (online only) lists the pathologic characteristics and molecular intrinsic subtype of patients with an RFI event.

Finally, we evaluated the ROR scores, available in 264 patients. Only nine samples (3.4%) were categorized as low risk, 56 (21.2%) were classified as intermediate risk, and the majority of tumors (199; 75.4%) were categorized as high risk. ROR scores on the basis of the intrinsic subtype are listed in Appendix Table A2 (online only). As expected, luminal A tumor samples showed significantly lower median ROR scores than HER2-enriched, luminal B, and basal-like tumor samples (50 v 76, 72.5, and 72.5, respectively;  $P < .001$ ). All tumor samples categorized as low risk by ROR score were luminal A. However, most luminal A tumors had an intermediate ROR score, and none of the luminal A tumors had high ROR score. In contrast, the majority of HER2-enriched, luminal B, and basal-like tumor samples were classified as high risk by ROR score.

Regarding TIPN, 230 patients had evaluable genetic data. In this subgroup, there were 24 cases of grade 2 or greater TIPN (10.4%); no grade 4 neurotoxicity was reported (in this cohort of patients or in the overall population of the study). Fifty of the planned 51 SNPs passed quality control



**FIG 2.** Disease-free survival (DFS). (A) Kaplan-Meier plot of DFS in the intention-to-treat population. (B) DFS according to hormone-receptor status. Abbreviations: neg, negative; Point est, point estimate; pos, positive.

**TABLE 3.** Estimated 3-Year, 5-Year, and 7-Year Rates for RFI, BCSS, and OS

Time (years)	RFI			BCSS			OS		
	No. of Events	No. at Risk	Rate (95% CI)	No. of Events	No. at Risk	Rate (95% CI)	No. of Events	No. at Risk	Rate (95% CI)
3	3	378	99.2 (98.4 to > 99.9)	0	386	—	1	386	99.7 (99.2 to > 99.9)
5	7	347	98.1 (96.8 to 99.5)	1	362	99.7 (98.1 to > 99.9)	5	362	98.7 (97.5 to 99.8)
7	9	120	97.5 (95.9 to 99.1)	3	127	98.6 (97.0 to > 99.9)	14	127	95.0 (92.4 to 97.7)

Abbreviations: BCSS, Breast Cancer-Specific Survival; OS, overall survival; RFI, Recurrence-Free Interval.

and were evaluated. One SNP, *rs3012437*, was associated with an increased risk of TIPN for grade 2 or greater TIPN after correction for age and body surface area ( $P = .024$ ; odds ratio, 2.1).

## DISCUSSION

This 7-year follow-up report of paclitaxel and trastuzumab for patients with small, node-negative HER2-positive breast cancer demonstrates few disease recurrences with even longer follow-up and further supports the use of this regimen for adjuvant therapy for this patient population. The 3-year and 7-year DFS in the APT trial were 98.7% and 93%, respectively, with just four distant recurrences at 7 years (1%). Many of the DFS events were contralateral cancers or unrelated deaths. When evaluating outcomes in relatively low-risk patients, it is important to acknowledge that DFS captures events that do not necessarily reflect a recurrence from the initial breast cancer. As we follow patients over time, the frequency of these events increases. As such, RFI, which includes invasive locoregional and distant recurrences and deaths as a result of breast cancer, may better describe the relevant event rate in this patient population. The 7-year RFI in the APT trial was 97.5%, suggesting few events related to the initial breast cancer diagnosis.

Molecular profiling of this subset of patients with small HER2-positive breast cancers by PAM50 identified all four intrinsic molecular subtypes. Most tumors were identified as HER2 enriched (66%), and, as expected, subtype distribution differed significantly by HR status. A greater percentage of HR-negative tumors were HER2-enriched and basal-like. However, the HER2-enriched subtype was the predominant subtype not only in the HR-negative

cohort but also in HR-positive tumors (84% and 58%, respectively). These results are in accordance with the PAMELA (PAM50 HER2-enriched Subtype as a Predictor of Response to Dual HER2 Blockade in HER2-positive Early Breast Cancer) trial,<sup>13</sup> where most tumors were classified as HER2 enriched (67%) as well. In contrast, the percentage of HER2-enriched subtype at baseline in the Cancer and Leukemia Group B (CALGB) 40601 study<sup>7</sup> was lower and was similar to percentages of luminal A and luminal B tumors. Moreover, among patients with HR-positive, HER2-positive tumors, the luminal subtypes were found to be the most prevalent.<sup>7</sup> The APT and PAMELA trials used the same nCounter platform to perform molecular profiling, whereas the RNA-seq method was used in the CALGB 40601 study. These data confirm that HER2-positive breast cancer is indeed a heterogeneous disease, not fully recapitulated by HR status, and that smaller HER2-positive tumors have a similar distribution of intrinsic subtypes as larger tumors. Therefore, the biology of these smaller tumors may not be dissimilar to larger tumors. Although it is known that intrinsic subtypes play a key role in determining response to anti-HER2 treatment,<sup>7,13</sup> data from this study are not able to assess the association of subtype with long-term outcomes, given the low event rate. Interestingly, though, the majority (71%) of the tumor samples were categorized as high ROR (> 60). Previous work in HR-positive, HER2-negative breast cancer suggests high ROR is associated with higher risk of recurrence;<sup>14,15</sup> however, given the low event rate seen in this study, these data may not be applicable to patients with small node-negative, HER2-positive tumors who receive therapy.

TIPN is an important toxicity that compromises paclitaxel treatment efficacy and patients' quality of life. To date, there are only minimally effective treatments, and there are no clinically implemented predictive biomarkers available for TIPN. Previously, SNPs associated with TIPN were identified using two large phase III adjuvant breast cancer trials, E5103 and E1199.<sup>12</sup> In the current study, we evaluated the same top 51 SNPs evaluated in the genome-wide association study from E5103<sup>12</sup> and found that *rs3012437*, which is in the uncharacterized *LOC154449* region of chromosome 6, is associated with the risk of grade 2 or greater TIPN. Thus, this represents, to our knowledge, the first independent association between *rs3012437* and the risk of TIPN warranting additional evaluation, because this

**TABLE 4.** Distribution of PAM50 Intrinsic Molecular Subtypes at Baseline in the Overall Cohort and According to HR Status

Subtype	Overall Cohort (n = 278)	HR-Positive (n = 196)	HR-Negative (n = 82)
HER2-enriched	183 (66)	114 (58)	69 (82)
Luminal B	38 (14)	38 (19)	2 (3)
Luminal A	35 (12)	33 (17)	0
Basal-like	22 (8)	11 (6)	11 (15)

NOTE. Data given as No. (%).

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

might ultimately affect treatment decision making in this population at high risk of TIPN.

The APT study has several strengths and limitations. It is a phase II study with a large sample size and long-term follow-up that reaffirms the results reported earlier. We are aware, however, that a randomized trial would have been ideal. As previously mentioned, there were feasibility concerns about the most appropriate control arm, because no standard of treatment existed at that time in this population. The higher frequency of HR-positive tumors in our study (67%) than in the pivotal adjuvant trastuzumab trials (51% to 54%) could have implications for late recurrences, because the risk of recurrence in the first years after diagnosis is higher in HR-negative tumors than in HR-positive ones. It is of interest, however, that a high percentage of the HR-positive tumors were also HER2 enriched. Whether these HR-positive and HER2-enriched tumors are at higher risk of late recurrence is unknown. In any case, the long-term follow-up data in this updated report confirm that these patients continue to do well and uphold this treatment strategy as adequate for small HER2-positive breast cancers. It is important to note, however, that this study does not provide data to support the use of trastuzumab-based therapy in all patients with small HER2-positive tumors. There will be patients, particularly most patients with pT1a

and some with pT1b, who may not require adjuvant trastuzumab-based chemotherapy, and a balance between a patient's risk of recurrence and potential toxicities must be considered. Work is ongoing to see if a potentially less-toxic therapy, such as trastuzumab emtansine (T-DM1), may be an alternative treatment strategy for patients with small HER2-positive tumors. The ATEMPT trial (Adjuvant Trastuzumab Emtansine vs Paclitaxel/Trastuzumab) (ClinicalTrials.gov identifier: [NCT01853748](https://clinicaltrials.gov/ct2/show/study/NCT01853748)) is an ongoing randomized phase II trial of T-DM1 versus adjuvant paclitaxel and trastuzumab for patients with stage I HER2-positive breast cancer that is comparing clinically relevant toxicities between the two arms and assessing DFS for patients receiving T-DM1. This study has completed accrual, and results are pending.

In conclusion, after a median follow-up of 6.5 years, patients with small, HER2-positive breast cancer treated with adjuvant paclitaxel and trastuzumab continued to demonstrate excellent outcomes. These long-term data support the use of adjuvant paclitaxel and trastuzumab as a treatment option for patients with stage I, HER2-positive breast cancer. This regimen represents an important step forward in de-escalating therapy to preserve quality of life while achieving excellent outcomes for patients with HER2-positive breast cancer.

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Seven-Year Follow-Up Analysis of Adjuvant Paclitaxel and Trastuzumab Trial for Node-Negative, Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer**

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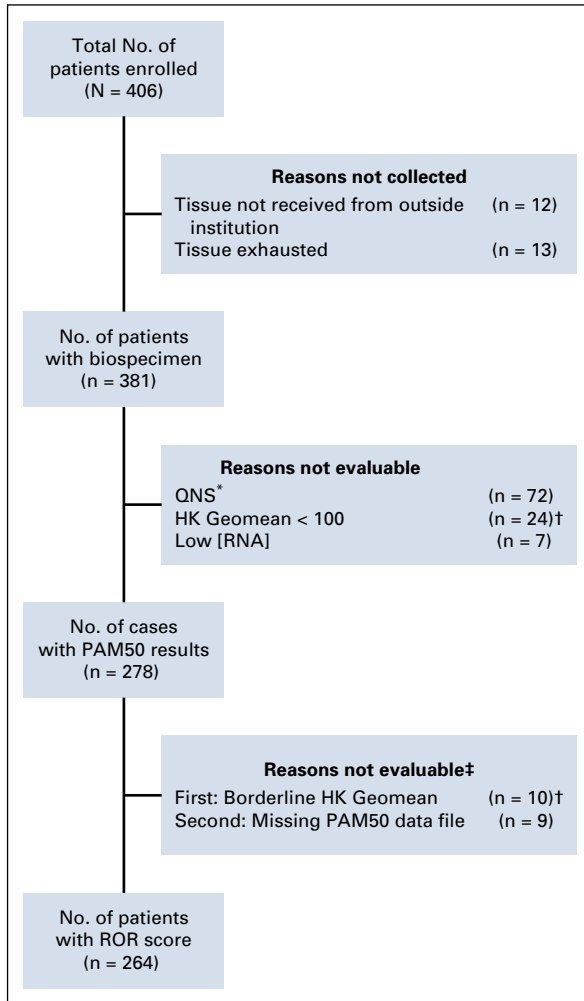
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## APPENDIX



**FIG A1.** Tumor sample analyses. (\*) Tumors less than 4 mm were excluded (insufficient invasive tissue). (†) NanoString set a pre-defined threshold to maintain the integrity of the subtyping call. A 100-count Geomean for the housekeeping genes (HKs) is the minimal amount needed to generate a confident subtype call. The algorithm requires data above the background to make a reasonable call of subtype, and HK was used as a marker for the rest of the targets. Cases with borderline HK Geomean were excluded from the risk of recurrence (ROR) score evaluation. (‡) Five cases previously incorrectly marked as failed subtyping were corrected and included in the ROR scoring. Therefore, there is a total discrepancy of 14 cases between the number of cases with PAM50 (Prosigna) results and number of cases with ROR scores. QNS, quantity not sufficient.

**TABLE A1.** Baseline Characteristics of Patients With an RFI Event

Age at Study Entry (years)	Histologic Grade	Hormone Receptor Status	Primary Tumor Size (cm)	Primary PAM50 Intrinsic Subtype	RFI Event	RFI PAM50 Intrinsic Subtype
40	3	Positive	1.5	QNS	Locoregional recurrence	QNS
41	3	Positive	0.8	QNS	Locoregional recurrence	HER2 enriched
72	3	Negative	1.9	QNS	Locoregional recurrence	HER2 enriched
56	2	Positive	0.8	QNS	Locoregional recurrence	QNS
49	3	Positive	0.8	Luminal B	Locoregional recurrence	Luminal A
58	3	Positive	1.6	Luminal B	Distant recurrence	QNS
46	3	Negative	1.2	HER2 enriched	Distant recurrence	HER2 enriched
55	3	Positive	0.9	Luminal B	Distant recurrence	Luminal B
73	3	Positive	2.5	HER2 enriched	Distant recurrence	QNS

Abbreviations: HER2, human epidermal growth factor receptor 2; QNS, quantity not sufficient; RFI, recurrence-free interval.

**TABLE A2.** ROR Scores on the Basis of the Intrinsic Subtype (N = 281)

Subtype	No. (%)	ROR, Median (range)	Low ( $\leq 40$ )	Intermediate (41-60)	High ( $> 60$ )
<b>HER2-enriched</b>	173 (65.5)	76 (46-100)	0	21	152
<b>Luminal B</b>	38 (14.4)	72.5 (51-94)	0	7	31
<b>Luminal A</b>	33 (12.5)	50 (8-59)	9	24	0
<b>Basal-like</b>	20 (7.6)	72.5 (51-91)	0	4	16

Abbreviations: HER2, human epidermal growth factor receptor 2; ROR, risk of recurrence.