

# HER2-neu Positivity in Patients with Small and Node-negative Breast Cancer (pT1a,b,N0,M0): A High Risk Group?

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**Abstract:** Human epidermal growth factor receptor 2 (HER2-neu) is an important prognostic factor associated with worsened disease-free survival and overall survival in breast cancer patients; however, the prognosis of T1a,b,N0,M0 HER2-neu positive breast cancer has not been clearly determined. Trastuzumab has become a critical component of the treatment of patients with HER2-neu positive tumors, but the effect of treatment in patients with small tumors and node-negative disease has not been evaluated in clinical trials. Current guidelines have category 3 recommendations to consider the use of adjuvant trastuzumab in women with node-negative tumors that are 0.6–1.0 cm, and state that physicians should balance the risks associated with the known trastuzumab toxicities and the uncertain benefits that may exist with such therapy in this group of patients.

The available data regarding the prognosis of patients with T1a,b,N0,M0 HER2-neu positive breast cancer is very limited. The purpose of this manuscript is to review the available literature in order to evaluate whether this group of patients represents a high risk group. Retrospective studies suggest that HER2-neu status is a powerful independent prognostic factor in T1a,b node-negative breast cancer. We believe that prospective studies and randomized clinical trials are strongly needed to clearly assess the impact of HER2-neu positivity in node-negative and subcentimeter tumors, and to determine if this group of patients can benefit from adjuvant trastuzumab treatment.

## Introduction

Breast cancer is the second most common cause of cancer death in the United States. In 2008, over 184,000 new cases were diagnosed.<sup>1</sup> The introduction of mammographic screening has led to an increase in the number of stage I breast cancers diagnosed.<sup>2,3</sup> According to the American Joint Committee version VI,<sup>4</sup> stage I breast cancer has a tumor size of less than or equal to 2 cm (T1), no lymph node metastases (N0), and no distant metastases (M0).

### Keywords

Breast cancer, HER2, node negative, small tumors, trastuzumab

T1 tumors are subdivided according to the greatest diameter into T1a ( $\leq 0.5$  cm), T1b ( $>0.5$  cm but  $\leq 1$  cm), and T1c ( $>1.0$  cm but  $\leq 2.0$  cm). According to data from the 2004 Behavioral Risk Factor Surveillance System,<sup>5</sup> 58.3% of U.S. women aged 40 years and older have had a mammogram within the past year, and 71.8% of those aged 50–64 years had a mammogram within the last 2 years.<sup>6</sup> Such an increase in the use of screening techniques has led to an increase in the detection of small tumors. The rate of T1 tumors diagnosed among women aged 50–69 years according to data from The Surveillance, Epidemiology, and End Results (SEER) program increased from 143.5 per 100,000 in 1990 to 163.5 per 100,000 in 1998; recent figures from the American Cancer Society indicate that from 1988–2000, the trend in diagnosis of smaller ( $\leq 2.0$  cm) tumors among women of all races continued to increase by 2.0% per year, and in 2000 was approximately 90 per 100,000.<sup>6,7</sup>

In general, patients with T1,N0,M0 tumors are considered to have very good prognosis, and in previously reported data, the 10-year relapse-free survival (RFS) rates after local therapy are 90% or greater.<sup>6,8-10</sup> Established prognostic factors have been described, and they include tumor size, tumor grade, histologic type, and hormone receptor status.<sup>11</sup> Other factors like younger age and fewer than 6 lymph nodes removed at the time of axillary dissection are associated with increased breast cancer mortality.<sup>12</sup> In recent times, HER2-neu has emerged as an important prognostic factor associated with worsened disease-free survival (DFS) and overall survival in breast cancer patients.<sup>13-15</sup> The HER2-neu gene is a member of a family of genes encoding transmembrane receptors for growth factors; its intracellular domain has tyrosine kinase activity and regulates important aspects associated with growth and differentiation.<sup>15,16</sup> Approximately 25% of breast carcinomas are HER2-neu positive.<sup>17</sup>

According to the American Society of Clinical Oncology/College of American Pathologists (CAP) Guideline Recommendations,<sup>18</sup> all invasive breast cancers should be assessed for HER2, preferably in a CAP-accredited laboratory or in a laboratory that meets the appropriate accreditation and proficiency. A positive HER2 result is an immunohistochemistry (IHC) staining of 3 (uniform, intense membrane staining of  $>30\%$  of invasive tumor cells), or a fluorescent in situ hybridization (FISH) result of more than 6 HER2 copies per nucleus or a FISH ratio (HER2 gene signals to chromosome 17 signals) of more than 2.2.

Trastuzumab (Herceptin, Genentech), a humanized monoclonal antibody against the extracellular domain of HER2-neu, has shown to dramatically improve DFS and overall survival in 5 randomized, phase III trials when administered in conjunction with adjuvant chemotherapy for mainly node-positive early-stage

breast cancer.<sup>14,19-22</sup> A recent meta-analysis<sup>23</sup> including data from these trials, showed a significant reduction in mortality, recurrence, metastases rates ( $P < .0001$  in all), and in second tumors other than breast cancer ( $P = .007$ ) when patients who received trastuzumab were compared to those that did not.

Trastuzumab has become a critical component of the treatment of patients with HER2-neu positive tumors; however, in patients with T1a,b,N0,M0 breast cancer, the available information is very limited. The purpose of this manuscript is to review the literature in order to evaluate if patients with small tumors, node-negative disease, and HER2-neu positivity represent a high risk group.

## Methods

We performed a Pubmed (National Library of Medicine) search looking for articles on the prognosis of patients with stage T1a,b,N0,M0 HER2-neu positive breast cancer published between June 2004 and June 2009. We identified articles using the terms “breast cancer/carcinoma”, “tumor size”, “small”, “one centimeter”, “T1a”, “T1b”, “node-negative”, “HER2, HER2/neu, or HER2-neu”, “trastuzumab”, and “herceptin”. Total retrieval was 88 references of full articles; of them, 28 full-length articles were retrieved. The relevant publications cited in the reference lists of the identified manuscripts were also searched.

To supplement the strategy, we also searched the abstracts presented at the 2006, 2007, 2008, and 2009 meetings of the American Society of Clinical Oncology, the Breast Cancer Symposium from the American Society of Clinical Oncology, and the San Antonio Breast Cancer Symposium. The principal investigators of the leading abstracts were contacted to obtain the complete data presented at the meeting, or, if possible, the in-press manuscript accepted by the journals. We also reviewed current guidelines for the management of breast cancer in the context of T1,N0,M0 HER2-neu positive disease.

After reviewing all documents and taking into consideration our specific search criteria, we focused on manuscripts and abstracts that included patients with T1a,b,N0,M0 HER2-neu positive breast cancer. Data from a clinical trial, 3 manuscripts,<sup>24-27</sup> 2 in-press manuscripts,<sup>28,29</sup> and 2 meeting presentations<sup>30,31</sup> were selected for this review. Table 1 shows a summary of the results of the retrospective analyses.

Among the included studies, relatively similar definitions of HER2-neu positivity were used. HER2 overexpressed tumors were those with IHC staining of 3+ (strong membranous staining in at least 10% of cells), or gene amplification found on FISH (gene copy/CEP-17 ratio  $\geq 2.0$ ).<sup>24,26-29</sup> For Joensuu and colleagues,<sup>25</sup> IHC 3+ expression was defined as strong intensity on

**Table 1.** Summary of Retrospective Studies Including Patients with T1(a,b),N0,M0 and HER2-neu Positive Breast Cancer

Study	N	% HER2 Over-expression	Follow-up	Outcome	Observations
Black <sup>30</sup>	T1a, 27 T1b, 47	N/A (100%)	5.6 y	<ul style="list-style-type: none"> <li>5-y DFS (for pT1a,b) 90.5%</li> <li>Distant metastases 8% at 5 y</li> <li>Local events 5.4% at 5 y</li> <li>Contralateral events 5.4% at 5 y</li> </ul>	
Joensuu <sup>25</sup>	T1a, 49 T1b, 264	12%	9.5 y	<ul style="list-style-type: none"> <li>9-y DFS (T1b grade 2 and 3 tumors) 67% vs 95% for HER2 positive and negative</li> </ul>	<ul style="list-style-type: none"> <li>HER2 in multivariate analysis was associated with worse prognosis (HR 2.56; 95% CI 1.05–6.23)</li> </ul>
Tovey <sup>26</sup>	T1, 230	6.9%	6.5 y	<ul style="list-style-type: none"> <li>T1 according to HER2 status (HR 8.99; 95% CI, 3.0–26.9)</li> <li>All cohort (T1,2): 5-y BCSS 68% in HER2 positive vs 96% in negative</li> </ul>	<ul style="list-style-type: none"> <li>Tumors were exclusively grade 1 and 2</li> </ul>
Chia <sup>24</sup>	T1a, 103 T1b, 225	6.4%  10.2% among all node negative	12.4 y	<ul style="list-style-type: none"> <li>10-y BCSS (T1a,b) 93.3% vs 94%, <math>P=.81</math> for HER2 positive and negative</li> <li>10-y BCSS (T1b) 68.4% vs 81.8%, <math>P=.31</math> for HER2 positive and negative</li> </ul>	<ul style="list-style-type: none"> <li>HER2 positivity was a predictor of survival in the complete cohort.</li> <li>Little impact of HER2 among hormone receptor–positive patients.</li> </ul>
Curigliano <sup>28</sup>	T1a, 85 T1b, 65	N/A (100%)	4.5 y	<ul style="list-style-type: none"> <li>5-y DFS (hormone receptor–positive): 92% vs 99%</li> <li>In hormone receptor–positive tumors, HER2-neu positivity associated w/ worse prognosis (HR 5.1; 95% CI, 1.0–25.7)</li> <li>5-y DFS (hormone receptor–negative): 91% vs 92%</li> </ul>	<ul style="list-style-type: none"> <li>Case-control study</li> <li>Similar risk of recurrence according to HER2 status in hormone negative tumors.</li> </ul>
Gonzalez-Angulo <sup>29</sup>	T1a, 323 T1b, 642  Subcohort 350	10%  6%	6.2 y	<ul style="list-style-type: none"> <li>5-y RFS 95% vs 77.1% (<math>P&lt;.0001</math>)</li> <li>5-y DRFS 86.4% vs 97.2% (<math>P&lt;.0001</math>) for HER2 positive and negative</li> <li>Multivariate analysis for recurrence according to HER2 status (HR 2.64; 95% CI, 1.44–5.0)</li> <li>In subcohort: 5-y RFS 87.4% vs 97.0%</li> </ul>	<ul style="list-style-type: none"> <li>Compared to hormone receptor–positive tumors, those with HER2 positivity (HR 5.09, 95 CI 3.17–19.22) and triple negative tumors (HR 3.89, 95% CI 2.56– 10.14) had higher risk of recurrence.</li> </ul>
Rodrigues <sup>31</sup>	96	N/A (100%)	2.1 y	<ul style="list-style-type: none"> <li>40 patients treated (37 had trastuzumab): 0 recurrences</li> <li>56 patients no chemo/trastuzumab: 5 (9%) recurrences</li> </ul>	<ul style="list-style-type: none"> <li>Treatment decision associated with tumor grade, mitotic index, and hormone receptor status.</li> </ul>

BCSS=breast cancer-specific survival; CI=confidence interval; DFS=disease free survival; DRFS=distant RFS; HR=hazard ratio; RFS=recurrence-free survival.

the cell membrane of the majority of cancer cells, FISH amplification was defined as 6 or more signals per nucleus in more than 50% of cancer cells, or presence of large gene copy clusters. A clear definition was not available in the meeting presentations by Black and associates<sup>30</sup> and Rodrigues and coworkers.<sup>31</sup>

Most of the documents expressed outcomes in terms of RFS or DFS. RFS was defined as the time from diag-

nosis to the date of first local or distant recurrence.<sup>24,29</sup> DFS was the length of time from surgery to relapse—secondary or primary (including contralateral breast)—or death.<sup>28</sup> Untch and coauthors<sup>27</sup> defined DFS as the time from randomization to occurrence of breast cancer at any site, development of ipsilateral or contralateral breast cancer (including ductal carcinoma in situ but not lobular carcinoma in situ), second non-breast malignant

disease other than basal cell or squamous cell carcinoma of the skin or cervical carcinoma in situ, or death from any cause. Distant DFS (DDFS) was the length of time from diagnosis to the occurrence of first distant recurrence or death.<sup>25,29</sup> Breast-cancer specific survival (BCSS) was assessed in some articles, and was defined as the time from the date of diagnosis of primary breast cancer to the date of death with breast cancer as the primary underlying cause.<sup>24,26</sup> Rates of metastatic disease, locoregional recurrence, contralateral breast cancer, and DFS were not clearly defined in the meeting presentations by Black and associates<sup>30</sup> and Rodrigues and coworkers.<sup>31</sup>

## Results

The treatment of breast cancer patients with small ( $\leq 1$  cm), node-negative, and HER2-neu positive tumors represents an area of controversy. Current guidelines recommend physicians to consider the use of adjuvant trastuzumab in women with node-negative tumors that are 0.6–1.0 cm.<sup>32</sup> This recommendation is considered category 3 because patients with tumors smaller or equal to 1 cm were not consistently included in the available randomized clinical trials, and because their overall risk of recurrence is considered to be relatively low despite their HER2-neu status. Therefore, recommendations are to balance the risks associated with the known trastuzumab toxicities and the uncertain absolute benefits that may exist with such therapy in this group of patients.

In order to determine the recurrence risk of patients with node-negative disease and HER2-neu positivity, Black and associates<sup>30</sup> evaluated 164 patients, 134 of which had pT1 (27 pT1a, 47 pT1b, and 60 pT1c) and 30 who had pT2 tumors. With a median follow-up of 67 months, the rates of distant metastases, locoregional events, contralateral events, and any events for patients with pT1a,b tumors were 8%, 5.4%, 5.4%, and 19%, respectively. Rates for pT2 tumors were 13%, 6.6%, 3.3%, and 23%. The 5-year DFS for pT1a,b tumors was 90.5%, very similar to the 5-year DFS observed in patients with pT1c (89.5%) tumors. Higher rates were seen in patients with pT2 tumors (79.5%).

In a nation-wide population-based study with data from the Finish Cancer Registry, Joensuu and colleagues,<sup>25</sup> evaluated the prognostic factors associated with patients with pT1,N0,M0 breast cancer. From the 1,208 patients with node-negative breast cancer who were identified, 852 (70.5%) had a primary T1 tumor and made up the final cohort of the study. Of the 852 patients, 49 (6%) had pT1a, 264 (31%) had pT1b, and 539 (63%) had pT1c tumors. With 9.5 years of follow-up, the multivariate analysis showed that histologic grade (2 or 3 versus 1; hazard ratio [HR]=2.36; 95% confidence interval [CI], 0.96–5.77), tumor size in mm (HR=2.65; 95% CI,

1.12–6.28), and HER2-neu positivity (HR=2.56; 95% CI, 1.05–6.23) were associated with poor prognosis. A subgroup analysis in patients with grade 2 and 3 tumors, which measured 0.6–1.00 cm, showed that patients with HER2-neu positive tumors had a higher risk of recurrence than those with HER2-neu negative disease (9-year DDFS, 67% vs 95%;  $P=.003$ ), suggesting that patients with HER2-neu positivity, despite having small tumors, represent a group with a higher risk of recurrence.

Similarly, in a retrospective cohort of node-negative breast cancer patients with low grade tumors, Tovey and colleagues<sup>26</sup> explored the effect of HER2 positivity on survival. They included 362 patients with grade 1 and 2 tumors: 78.1% had positive hormone receptor status and 6% had HER2-neu positive tumors (60% of the HER2-neu positive tumors were also hormone receptor status-positive). Five-year BCSS rates were 68% for the patients that had HER2-neu positive tumors compared with 96% for the patients with HER2-neu negative disease ( $P<.001$ ). These results remained significant when a multivariate model including grade, size, age, chemotherapy treatment, and hormone receptor status was built ( $P<.001$ ). A subgroup analysis in the 230 patients with tumors smaller than 2.0 cm continued to indicate the adverse prognosis of patients with HER2-neu positivity (HR=8.99; 95% CI, 3.0–26.9). Of all the patients in this cohort, 230 (63.5%) had T1 tumors; and in this subgroup of patients, there were only 16 (6.9%) with HER2-neu positive tumors. Therefore, an analysis in patients with subcentimeter tumors could not be performed given the small sample size.

With relatively different results, Chia and associates<sup>24</sup> identified 2,026 cases of node-negative breast cancer. Using tissue microarray, they evaluated HER2-neu positivity as a prognostic factor in this group of patients. Two-hundred and six patients (10.2%) had HER2-neu positive tumors. The authors found that HER2-neu was significantly associated with higher grade tumors, ductal histology, and hormone receptor-negative status ( $P<.001$  in all cases). In a multivariate analysis including all the patients in the cohort, HER2-neu positivity was an independent poor prognostic factor for breast cancer relapse (odds ratio [OR], 1.71;  $P=.01$ ) and breast cancer death at 10 years (OR, 2.03;  $P=.003$ ). Within the T1,N0,M0 cohort ( $n=1,245$ ), HER2-neu was not significantly associated with RFS or DRFS, but the 10-year BCSS was worse in the HER2-neu positive cohort versus the HER2-neu negative (81.2% vs 90.1%;  $P=.31$ ). When the authors focused on the 328 patients who had tumors measuring 0.1–1.0 cm, a trend towards worse RFS for patients with HER2-neu positive tumors was seen; however, there were no differences in 10-year BCSS (93.3% vs 94.0%;  $P=.80$ ). When interpreting these results, it is important to take in to account that despite the large cohort size,

only 21 (6.4%) patients with subcentimeter tumors were HER2-neu positive. The authors also focused on the even smaller group of patients with tumors between 0.6 and 1.0 cm who did not receive any adjuvant systemic treatment (n=225). They found that patients with HER2-neu positive tumors (n=23) tend to have a worse outcome than patients without them (10-year RFS, 68.4 vs 81.8%;  $P=.312$ ). Additionally, when the authors performed an analysis according to hormone receptor status in stage I patients, they observed that among hormone receptor-positive tumors, HER2-neu positivity seemed to have little impact on RFS or DRFS. In hormone receptor-negative patients, the HER2-neu positive tumors had a 10% worse RFS and DRFS compared to HER2-neu negative tumors.

As it has been pointed out, the number of patients with subcentimeter tumors in the previously discussed articles was small. There are 2 manuscripts in press evaluating the prognosis associated specifically with T1a,b,N0,M0 HER2 positive breast cancer. Curigliano and colleagues<sup>28</sup> performed a case-control analysis that included 150 patients with node-negative, HER2-neu positive, subcentimeter tumors. Patients did not receive adjuvant chemotherapy or trastuzumab. Cases were matched to patients with HER2-neu negative tumors by hormone receptor status (1:1 for the hormone receptor-negative patients and 1:2 for the hormone receptor-positive), age (within 5 years), and year of diagnosis (within 2 years); the final analysis included 379 patients. Among the 150 cases, 79 (53%) had hormone receptor-positive tumors, 85 (56.6%) were classified as pT1a, and 65 (43.3%) as pT1b. The 5-year DFS among the hormone receptor-positive group was 92% in the patients with HER2-neu positive tumors and 99% in the patients with HER2-neu negative disease. A multivariate analysis adjusting for stage among patients with hormone receptor-positive tumors showed that patients with HER2-neu positivity have worse prognosis (HR=5.1; 95% CI, 1.0–25.7). The results suggest, contrary to what Chia and associates<sup>24</sup> observed, that the HER2-neu status is an important determinant of the biology and the prognosis of this, otherwise considered, good prognosis group of patients. On the other hand, among the hormone receptor-negative patients, the 5-year DFS rates were 91% and 92% for the HER2-neu positive and negative tumors, respectively. The observed lack of prognostic value associated with HER2 status in this group is likely related to the high risk of recurrence seen in patients with triple negative tumors. The overall survival in patients with HER2-neu positive tumors was similar irrespective of their hormone receptor status ( $P=.93$ ).

When the same analyses were done according to pT1a and pT1b status, similar results were seen. In patients with pT1a hormone receptor-positive tumors, those with HER2-neu positivity had a 5-year DFS of

88% compared to 97% in those with HER2-neu negative tumors. In pT1b hormone receptor-positive tumors, the 5-year DFS rates were 95% and 99%, respectively. For the hormone receptor-negative tumors, the 5-year DFS rates were 93% and 87% for pT1a, and 85% and 94% for pT1b in HER2-neu positive and negative tumors. HER2-neu positivity remained associated with a poor prognosis after adjustment for tumor size and hormone receptor status (HR=5.1; 95% CI, 1.0–25.7).

Our group<sup>29</sup> identified 965 women with newly diagnosed node-negative breast cancer with subcentimeter tumors. Three-hundred and twenty three (33.5%) patients had pT1a and 642 (66.5%) had pT2 tumors. Ninety-eight (10%) patients had HER2-neu positive breast carcinomas, which were associated with younger age, pT1a tumors, high nuclear grade, and no hormone receptor-positive disease ( $P<.001$  in all). Patients with HER2-neu positivity had worse 5-year RFS than HER2-neu negative patients (92.0% vs 77.1%;  $P<.0001$ ). Five-year DRFS was 86.4% for patients with HER2-neu positive tumors compared to 97.2% in those with HER2-neu negative disease ( $P<.0001$ ). After adjustment for hormone receptor status, tumor size, and nuclear grade, patients with HER2-neu positive breast cancer had a significantly higher risk of recurrence (HR=2.68; 95% CI, 1.44–5) and distant recurrence (HR=5.3; 95% CI, 2.23–12.62). When patients were grouped according to breast cancer subtype, we found that patients with HER2-neu positive tumors (HR=5.09; 95% CI, 3.17–19.22) and with triple negative disease (HR=3.89; 95% CI, 2.56–10.14) had a higher risk of recurrence compared to the group of patients with hormone-positive disease. In order to show reproducibility, data on 350 patients treated at other institutions were obtained. Of the 350 patients, 21 (6%) had HER2-neu positive breast carcinomas. Five-year RFS rates were 87.4% and 97.0% for the HER2-neu positive and HER2-neu negative tumors, respectively. The differences in prognosis according to breast cancer subgroup were also seen in the patients from other institutions; patients with HER2-neu positive tumors had worse RFS than patients with triple negative or hormone receptor-positive tumors ( $P=.002$ ). These results confirmed prior observations, suggesting that patients with node-negative, HER2-neu positive, subcentimeter tumors have a high risk of relapse. Therefore, such patients should be considered for participation in randomized clinical trials where the effect of HER2 targeted therapies is evaluated.

A subgroup analysis of patients treated in the HERA trial was recently published.<sup>27</sup> The HERA trial is a multicenter randomized trial comparing 1 or 2 years of trastuzumab treatment versus observation after standard chemotherapy in patients with HER2-neu positive breast cancer. From the 3,401 randomized patients, 1,099 had node-negative disease, and of these, 60 had tumors smaller

than 1.0 cm, 33 had tumors that equaled 1.0 cm, and 510 had tumors ranging from 1.1–2.0 cm (T1c). When analyzing the effect of the node-negative and T1c tumors subgroup (252 patients randomized to trastuzumab and 258 to observation), the 3-year DFS was 91.3% (95% CI, 85.3–97.2) for the trastuzumab group and 86.7% (95% CI, 80.5–92.9) for the observation group with an HR of 0.53 (95% CI, 0.26–1.07). This observation is very important, as it demonstrated that the benefit of trastuzumab appears to extend even to this relatively favorable prognosis group, and presents the possibility to explore the effect of adjuvant trastuzumab even in patients with tumors that are smaller than 1 cm.

Rodrigues and coworkers<sup>31</sup> reported the results of a retrospective series evaluating the efficacy of trastuzumab treatment in patients with node-negative, HER2-neu positive, subcentimeter breast cancer. Ninety-six patients diagnosed from 2000–2008 were identified; 40 of these patients (42%) received chemotherapy, which was trastuzumab-based in almost all patients (37/40). The decision of treating this group of patients had a statistically significant association with negative hormone receptor status, higher grade, high mitotic index, and year of diagnosis. With short follow-up (25 months), no evidence of recurrence was seen in patients treated with trastuzumab or chemotherapy (considered mainly “poor” prognosis); however, in 5 of the 56 patients (9%) who did not receive adjuvant treatment (considered mainly “good” prognosis), local or distant recurrences were observed (long rank test  $P=.13$ ). The recurrences occurred in patients with T1b tumors, and 4 of them had negative hormone receptor status. The majority of patients with positive hormone receptor status (80%) were treated with hormone therapy.

## Discussion

Traditionally, breast cancer patients with node-negative disease and small tumors have been considered to have good prognosis despite having HER2-neu positive tumors. The specific prognosis and best treatment approach for patients with T1a,b,N0,M0 HER2-neu positive breast cancer have not been clearly determined and represent an area of controversy. In this review we present the retrospective data available in order to evaluate whether this group of patients represents a high risk group.

In the studies included in this review, HER2-neu positivity was seen in 6–12% of the cases, which is an interesting observation, as HER2-neu positive tumors usually represent between 20 and 30% of breast cancers.<sup>17</sup> This may be an indication of a smaller malignancy potential of the pT1,N0,M0 breast cancer subgroup. It is well known that the determination of HER2-neu status can be inadequate in up to 20% of cases<sup>33,34</sup>; in

the discussed studies, the methods used to determine HER2-neu positivity were very similar, but they were not identical, making misclassification impossible to rule out. It is also possible that selection bias occurred, as the discussed studies have the limitations inherent to retrospective analyses. Furthermore, small absolute number of HER2-neu positive tumors may have contributed to the discrepancies seen. However, despite these limitations and modest available data, it seems that HER2-neu status is a powerful independent prognostic factor in T1a,b node-negative breast cancer.

In the study by Tovey and colleagues,<sup>26</sup> the low frequency of tumors with HER2-neu positivity is likely related to the fact that the authors included only patients with grade 1 and 2 breast cancer. In different series that included patients with node-negative disease, HER2-neu status has been associated with tumor grade.<sup>24,29,35,36</sup> By limiting their analysis to low grade tumors, the authors potentially also selected for a population less likely to have HER2-neu positive tumors. Despite this limitation, this observation suggests that in tumors with otherwise good prognostic features (low grade tumors, node-negative, positive hormone receptor status), HER2-neu positivity adversely affects prognosis, suggesting that HER2-neu is a determinant of the biology of these tumors.

The relationship between HER2-neu positivity and hormone receptor status is not clearly defined. The Trans-ATAC study<sup>37</sup> showed that approximately 10% of hormone receptor–positive tumors are also HER2-neu positive; results suggest that the benefit from tamoxifen was smaller in this group of patients. Similarly, a subgroup analysis of the BIG 1-98 study<sup>38</sup> revealed that among patients with hormone receptor–positive disease, those with HER2-neu positive tumors have a worse prognosis. These observations are likely secondary to a crosstalk between HER2-neu and hormone receptors that could induce resistance to endocrine treatment. The lack of prognostic value for HER2 status seen in patients with hormone receptor–negative disease is likely due to the high risk of recurrence associated to triple negative tumors. A multivariate analysis of our own data<sup>29</sup> revealed that despite adjusting for hormone receptor status, patients with HER2-neu positive tumors have worse outcomes than those who do not overexpress HER2-neu. Looking at breast cancer subgroups, we observed that compared to hormone receptor–positive tumors, those who are HER2-neu positive or triple receptor–negative are associated with worse outcomes.

Chia and colleagues<sup>24</sup> observed that among hormone receptor–positive tumors, HER2-neu positivity seemed to have little impact on outcome, whereas in hormone receptor–negative patients, HER2-neu positive tumors had a 10% worse RFS and DRFS. This contradicts the results of Curigliano and associates.<sup>28</sup> In a large cohort

of patients, they observed that HER2-neu positivity was associated with worse outcome, but this was particularly evident in patients with hormone receptor–positive disease. Among the studies presented in this review, the report by Chia and colleagues<sup>24</sup> has the longest follow-up (12.4 years). It is possible that late recurrences from patients with hormone receptor–positive disease account for the lack of difference in outcome among this subgroup of patients. Studies with longer follow-up are needed, as they will hopefully provide more information on the interaction between HER2-neu positivity and positive hormone receptor status. Undoubtedly, hormone receptor status influences outcomes. However, in the presence of HER2-neu positivity this contribution is likely minimal, as HER2-neu overexpression or amplification possibly drives the biology of the tumor.

The meeting presentation by Rodrigues and coworkers<sup>31</sup> shows the efficacy of trastuzumab treatment in patients with node-negative, HER2-neu positive, subcentimeter breast cancer. Despite short follow-up and clear selection bias (high risk patients were the ones selected for treatment), lower rates of recurrence were seen in patients treated with trastuzumab. Longer follow-up is needed to confirm these results, though they suggest that there is a benefit in treating patients with high risk features, despite having small, node-negative tumors, leading to the belief that targeted therapies against HER2-neu should be considered in this group of patients. As mentioned previously, the HERA trial included 1,099 patients with node-negative disease. Patients with T1c tumors treated with trastuzumab had better 3-year DFS than those who did not receive trastuzumab.<sup>27</sup> This observation demonstrates that the benefit of trastuzumab appears to extend to this group of patients, and presents the possibility of exploring the effect of adjuvant trastuzumab in patients with smaller tumors.

The BIRG006 is a multicenter phase III clinical trial that included node positive and high risk node-negative patients.<sup>21</sup> The study randomized 3,222 patients to receive doxorubicin and cyclophosphamide followed by docetaxel (ACT) versus doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC-TH) versus docetaxel, carboplatin, and trastuzumab (TCH). The subset of node-negative patients had 0 of at least 6 resected lymph nodes or negative sentinel node biopsy, and at least one of the following risk factors: tumor size greater than 2 cm, negative estrogen receptor and progesterone status, histologic grade 2–3, or age less than 35 years. Twenty-nine percent of the patients in each group had node-negative disease. In a preliminary subgroup analysis, DFS was improved in the 2 arms that included trastuzumab when compared to AC-T (AC-TH: HR=0.32, 95% CI, 0.17–0.62; TCH: HR=0.47, 95% CI, 0.26–0.83). The

4-year DFS rates were 94% for AC-TH, 93% for TCH, and 86% for AC-T. Based on these preliminary results, it seems that the benefit from trastuzumab treatment is present in high risk node-negative patients. The final analysis of this trial is eagerly awaited. It will hopefully include a better characterization of the node-negative patients, likely providing important information on the management of patients with small tumors and node-negative disease.

Different clinical trials are actively enrolling patients with HER2-neu positive, subcentimeter, node-negative breast cancer. The Adjuvant Paclitaxel and Trastuzumab for Node-Negative and HER2-Positive Breast Cancer Trial (NCT00542451) is a phase II nonrandomized, open-label clinical trial including patients with tumors of less than 3 cm and node-negative disease. Four hundred expected participants will receive a paclitaxel and trastuzumab combination weekly for 12 weeks, followed by trastuzumab every 3 weeks for 40 weeks. The BETH study: Treatment of HER2-Positive Breast Cancer with Chemotherapy Plus Trastuzumab vs. Chemotherapy Plus Trastuzumab Plus Bevacizumab (NSABP B-44-1, NCT00625898) is a multicenter, phase III, randomized, 4-arm, open-label clinical trial randomizing patients to receive docetaxel, carboplatin, and trastuzumab versus the same combination plus bevacizumab; or paclitaxel plus trastuzumab followed by 5-fluorouracil plus epirubicin plus cyclophosphamide followed by trastuzumab versus the same combination plus the addition of bevacizumab during the paclitaxel and maintenance trastuzumab administration. This clinical trial is planning to enroll 3,500 patients and will include patients with pT1-3, pN0-N3 disease. Node negative participants will need to have at least one of the following high risk features: tumor size greater than 2 cm, hormone receptor–negative status, high grade, or age less than 35 years.

Prospective studies and randomized clinical trials are strongly needed and the results will be eagerly awaited, as they will clearly assess the prognostic impact and the treatment effect of trastuzumab in patients with HER2-neu positive, node-negative, and subcentimeter tumors.

## Conclusions

With the advent of newer diagnostic techniques, it is very likely that the number of patients diagnosed with small tumors will increase, making the management of node-negative HER2-neu positive tumors a clinical challenge. HER2-neu positivity is relatively uncommon in small, node-negative breast cancers, representing 10% or fewer of all cases. Despite their low frequency, tumors with such characteristics represent a high risk group. Therefore, we believe that targeted therapies against HER2-neu should be considered in this group of patients.

Many questions remain unanswered regarding the interaction between hormone receptor and HER2-neu status in patients with small tumors and node-negative disease. It has yet to be determined what benefit patients with HER2-neu positive tumors will obtain with standard trastuzumab treatment, and whether this benefit outweighs the risks. It is also unclear if these patients will require long-term treatment (52 weeks), or if a less intense schedule will be appropriate. Prospective studies and randomized clinical trials are urgently needed to clearly assess the prognostic impact of HER2-neu positivity in patients with node-negative, and subcentimeter tumors in order to clearly determine if this group of patients can benefit from adjuvant HER2-neu-targeted treatment

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