Small HER2-positive, node-negative breast cancer: who should receive systemic adjuvant treatment?

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Adjuvant treatment of early-stage breast cancer with combined trastuzumab and chemotherapy has become standard in patients with HER2-positive tumors and a diameter of >1 cm or positive lymph nodes. Currently, there are no data directly supporting the use of adjuvant treatment, including trastuzumab, in patients with HER2-positive tumors, a diameter of ≤1 cm and no nodal involvement (pT1a,bpN0M0). However, 6%–10% of these small tumors are HER2 positive, and there is good evidence for an inferior clinical outcome in these patients, with recurrence rates of up to 30% after 5–10 years. Assumed that the relative risk reduction is similar to larger tumors, the absolute benefit should be large enough to consider adjuvant treatment. This review addresses current data regarding the prognosis of small HER2-positive tumors and discusses potential factors to individualize adjuvant treatment in patients with small HER2-positive tumors.

Key words: adjuvant treatment, breast cancer, HER2-overexpression, small tumors, trastuzumab

review

Small HER2-positive tumors

HER2 overexpression is found in 15%–20% of early-stage breast carcinomas [1]. The HER2-blocking antibody trastuzumab has—in conjunction with chemotherapy—become the standard adjuvant treatment in patients with HER2-positive tumors and a diameter of >1 cm or positive lymph nodes, based on evidence from large clinical trials [2–9]. In these trials, patients with breast cancer and a diameter of ≤1 cm and no nodal involvement (referred to as ‘small tumors’ throughout this article) were usually excluded. However, small node-negative tumors are increasingly seen by the clinician, mainly as a consequence of mammography screening, and clinical decision making on adjuvant systemic treatment will have to be based on indirect evidence. Although there is no clear evidence for trastuzumab not to be active when given in small HER2-positive tumors, the absolute benefit is expected to be smaller as compared with larger tumors. This review will address aspects of prognosis and potential indications for adjuvant treatment in patients with small HER2-positive tumors.

Prognostic role of HER2 in patients with pT1pN0M0 breast cancer

Small breast carcinomas are—on average—considered to have a favorable prognosis, especially when screen detected, and adjuvant systemic treatment is frequently omitted in these patients. The seven studies providing data on the prognostic role of HER2 in patients with small node-negative tumors not receiving adjuvant trastuzumab are summarized in Table 1 [10–16].

Press et al. [10] found HER2 amplification by FISH in 13%–19% of breast carcinomas diagnosed at three sites. When adjusting for known prognostic factors (patient age, tumor stage, hormone receptor status and histological grading), HER2 amplification was a significant and independent prognostic factor, with a relative risk of 3.1 (95% CI 1.3–7.5) for 2-year relapse-free survival (RFS) and 5.5 (95% CI 2.2–13.8) for disease-related death. In patients with tumors ≤1 cm, HER2 amplification was a significant and independent prognostic factor for time to recurrence and disease-related death, with a relative risk of 4.6 (95% CI 1.03–20.6) and 11.1 (95% CI 1.01–122.8), respectively [10]. In 2003, the Finish study group reported several prognostic factors in pT1pN0M0 breast tumors diagnosed in 1991/1992 in five well-defined geographical regions comprising roughly 50% of the Finish population [11]. A minority of 5% of the patients studied received adjuvant systemic treatment. Of the 1208 node-negative tumors, 852 (71%) tumors were ≤20 mm. T-stage distribution of these pT1pN0 tumors was as follows: 49 (6%) pT1a, 264 (31%) pT1b and 539 (63%) pT1c. In pT1pN0 tumors with available HER2 status (569 cases for immunohistochemistry and 548 for FISH), 13% were HER2 positive, irrespective of the detection method. Nine-year distant disease-free survival (DDFS) was significantly higher in patients with HER2-negative tumors as compared with HER2-positive tumors (89% versus 73%, P = 0.0003). Apart from the HER2 status, tumor size (in millimeter) and possibly grade (G2 or 3 versus G1) were significant and independent prognostic factors. In patients with pT1a,bpN0 tumors and moderate or poor differentiation, 9-year DDFS was
### Table 1. Prognostic role of HER2 in patients with node-negative breast cancer ≤1 cm

<table>
<thead>
<tr>
<th>Study population (total No.)</th>
<th>Study population (total No.)</th>
<th>pT1a,b tumors</th>
<th>HER2+ of total population</th>
<th>HER2+ in pT1a,b tumors</th>
<th>Adj. treatment in pT1a,b tumors</th>
<th>End point</th>
<th>Outcome in pT1a,b tumors</th>
<th>HR, HER2+/HER2− (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node-negative tumors, only pT1a,b</td>
<td>MDACC [14]</td>
<td>pT1a,b pN0M0 (965)</td>
<td>965 100</td>
<td>98 10</td>
<td>98 10</td>
<td>526 HT</td>
<td>55 5-year RFS</td>
<td>94 77</td>
</tr>
<tr>
<td>EIO [16]</td>
<td>pT1a,b pN0M0 (2130)</td>
<td>379 100</td>
<td>150 7</td>
<td>150 7</td>
<td>202 HT</td>
<td>53 5-year DFS</td>
<td>99 92</td>
<td>2.4 (P = 0.09)</td>
</tr>
</tbody>
</table>

#### Study population (total No.)

<table>
<thead>
<tr>
<th>Study population (total No.)</th>
<th>Study population (total No.)</th>
<th>pT1a,b tumors</th>
<th>HER2+ of total population</th>
<th>HER2+ in pT1a,b tumors</th>
<th>Adj. treatment in study population</th>
<th>End point</th>
<th>Outcome in study population</th>
<th>HR, HER2+/HER2− (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node-negative tumors</td>
<td>British Columbia Cancer Agency [13]</td>
<td>pT1-3 N0 M0 (2026)</td>
<td>326 16</td>
<td>206 10</td>
<td>21 6</td>
<td>373 HT</td>
<td>18 10-year BCSS</td>
<td>86 76</td>
</tr>
<tr>
<td>Glasgow Royal Infirmary [15]</td>
<td>pT1-2 N0 M0 G1–2 (362)</td>
<td>n.a. 22</td>
<td>6</td>
<td>n.a.</td>
<td>188 HT</td>
<td>2 5-year BCSS</td>
<td>96 68</td>
<td>5.65 (P &lt; 0.0001)</td>
</tr>
<tr>
<td>Finish Study Group [11]</td>
<td>pT1 N0 M0 (852)</td>
<td>313 37</td>
<td>65 12</td>
<td>n.a.</td>
<td>31 HT</td>
<td>9 9-year DDFF</td>
<td>89 73</td>
<td>2.56 (P = 0.04)</td>
</tr>
<tr>
<td>Dana Farber Cancer Institute [12]</td>
<td>pT1-2 N0 M0 HER2+ (164)</td>
<td>74 45</td>
<td>164 100</td>
<td>74 100</td>
<td>40 HT</td>
<td>54 5-year DFS</td>
<td>– 91</td>
<td>n.a.</td>
</tr>
<tr>
<td>Norris Comprehensive Cancer Center [10]</td>
<td>pN0M0 (242)</td>
<td>55 23</td>
<td>46 19</td>
<td>–</td>
<td>None</td>
<td>2-year RFS</td>
<td>94 83</td>
<td>3.1 (P &lt; 0.05)</td>
</tr>
</tbody>
</table>

*The total number of patients included.

*Matched-pair patients.

*Proportion of patients from the matched-pair analysis.

*Estrogen receptor-positive patient subgroup.

*Estrogen receptor-negative patient subgroup.

*HR for HER overexpression was 5.2 (95% CI 1.0–25.7) in the subgroup of patients with endocrine-responsive tumors (ER+ and/or PgR+).

*Statistically significant difference.

*By FISH.

*In patients with tumors <1 cm.

*Five-year DFS was 91% for pT1a-b (small) tumors, 90% for pT1c and 80% for pT2 tumors.

CI, confidence interval; BC, breast cancer; BCSS, breast cancer-specific survival; CHT, chemotherapy; CMF, cyclophosphamide/methotrexate/5-FU; DDFF, distant disease-free survival; DFS, disease-free survival; EIO, European Institute of Oncology; ER, estrogen receptor; HR, hazard ratio; HT, hormonal treatment; MDACC, MD Anderson Cancer Center; PgR, progesterone receptor expression; RFS, relapse-free survival; Tx, treatment.
higher for patients with HER2-negative as compared to HER2-positive tumors (95% versus 67%, respectively) [11]. In a retrospective study from 2006, Black et al. [12] reported the risk for disease recurrence in 164 node-negative HER2-positive tumors ≤5 cm, including 74 pT1a,b tumors and 60 pT1c tumors. In patients with pT1a,b tumors, 34% received adjuvant chemotherapy and 54% endocrine therapy. At a follow-up of 5 years, disease-free survival (DFS) was 91% in patients with pT1a,b tumors, 90% in patients with pT1c tumors and 80% in patients with pT2 tumors. Patients with HER2-positive tumors pT1a,b had a moderate risk for disease recurrence, similar to pT1c tumors. It is unknown whether this might be due to more frequent use of adjuvant chemotherapy in patients with pT1c tumors. In patients with pT1a,b tumors, there were fewer recurrences in patients receiving chemotherapy (1 of 25 patients, 4%) as compared with patients who received no chemotherapy (7 of 42, 17%) [12]. In a large Canadian series of 2026 patients with pT1-3 node-negative tumors, patients with HER2-positive tumors had a lower 10-year RFS (66% versus 76%, P = 0.01), distant RFS (71% versus 82%, P = 0.004) and breast cancer-specific survival (BCSS) (76% versus 86%, P = 0.001) as compared with patients with HER2-negative tumors [13]. No patient had adjuvant trastuzumab. In patients with pT1pN0 tumors (n = 1245), HER2 was not associated with a significantly worse RFS and distant RFS, only BCSS was significantly inferior in patients with HER2-positive as compared with HER2-negative tumors (81% versus 90%, P = 0.03). HER2 status had no significant impact on clinical outcome in patients with estrogen receptor-positive tumors. However, patients with estrogen receptor-negative, HER2-positive tumors had a 10% lower RFS and distant RFS as compared with estrogen receptor-negative, HER2-negative tumors. Small tumors pT1a,bpN0 were found in 326 patients, whereof 268 patients (82%) did not receive adjuvant systemic therapy. Only 21 of these 326 pT1a,b tumors (6%) and 16 tumors of the 268 patients without adjuvant therapy (6%) were HER2 positive. There was a trend toward worse RFS for patients with HER2-positive tumors, but there was no difference in 10-year BCSS by HER2 status. Results were similar for patients with or without adjuvant treatment. In patients with pT1b tumors not receiving any adjuvant systemic treatment (n = 225), 10-year RFS was lower in HER2-positive as compared with HER2-negative tumors (68% versus 82%, P = 0.31), although not significant. Due to the limited number of cases, the authors of this study concluded that larger studies would be needed to confirm the prognostic impact of HER2 status in pT1a,bpN0 tumors, particularly within the separate hormone receptor subgroups [13]. A series from MD Anderson Cancer Center included 965 patients with small node-negative tumors not receiving adjuvant trastuzumab or chemotherapy and diagnosed from 1990 to 2002 [14]. In this cohort, 98 (10%) had HER2-positive tumors, 742 (77%) hormone receptor-positive tumors and 125 (13%) had triple-negative tumors, 323 patients (33%) had pT1a and 642 (67%) had pT1b tumors. HER2 positivity was associated with younger age, pT1a tumors, high nuclear grade and hormone receptor-negative tumors (P < 0.001 for all comparisons). In the HER2-positive group, 43 (44%) patients had pT1a and 35 (36%) patients had pT1b tumors. Sixty patients were both HER2 positive and hormone receptor positive. HER2 overexpression was associated with a significantly inferior DFS (77% versus 94%, P < 0.0001) and DDFS (86% versus 97%, P < 0.0001) at 5 years as compared with HER2-negative tumors, and this was independent of other prognostic factors. After adjustment for nuclear grade, tumor size and hormone receptor status, HER2-positive patients had a significantly higher risk of recurrence [hazard ratio (HR) 2.68, 95% confidence interval (CI) 1.44–5, P = 0.002] and distant recurrence (HR 5.3, 95% CI 2.23–12.62, P = 0.0002) compared with those with HER2-negative tumors. When patients were clustered according to both the HER2 and the hormone receptor status, patients with HER2-positive disease had 5.1 times the risk of recurrence (95% CI 2.56–10.14, P < 0.0001) and patients with triple-negative tumors had 3.9 times the risk of recurrence (95% CI 2.56–10.14, P < 0.0001) as compared with patients who had hormone receptor-positive disease. There were no differences in RFS estimates in patients with HER2-positive and hormone receptor-negative tumors compared with HER2-positive hormone receptor-positive tumors. There were recurrences in 13 of 60 patients (21%) who had HER2-positive hormone receptor-positive disease and in 8 of 38 patients (21%) who had HER2-positive hormone receptor-negative disease. In patients with HER2-positive hormone receptor-positive disease (n = 60), 7 of the 13 recurrences were in patients without adjuvant endocrine treatment and 6 in patients receiving endocrine treatment. Endocrine treatment in patients without recurrence was not reported [14]. The results of the MD Anderson Group were confirmed by a cohort of 350 small node-negative tumors from Jules Bordet Institute and GH Leoben, showing 5-year RFS (87% versus 97%) and DRFS (92% versus 97%) to be lower in HER2-positive as compared with HER2-negative tumors [14]. In another retrospective analysis from the Glasgow Royal Infirmary, 362 node-negative G1–2 breast carcinomas were selected out of a larger series [15]. HER2 overexpression was an independent predictor for an inferior clinical outcome, and this was also true when patients were split into subgroups by hormone receptor status, tumor size and patient age. HER2 overexpression or gene amplification increased the risk for dying in patients with ER-positive tumors (in the presence of endocrine treatment) and ER-negative tumors (HR 6.05 and 7.97, respectively). However, no data were given for small tumors [15]. A recent survey from the European Institute of Oncology (EIO) included 150 small node-negative, HER2-positive tumors out of a series of 2130 patients with pT1a,bpN0 tumors receiving surgery at the EIO from 1999 to 2006 [16]. Among these 150 patients, 85 tumors were classified as pT1a (57%) and 65 as pT1b (43%). Patients were matched by receptor status, age and year at surgery on a 1 : 1 ratio for the hormone receptor-negative group and on a 1 : 2 ratio for the hormone receptor-positive group. Matched-pair analysis was carried out on a total of 379 patients with pT1a,bpN0 tumors. In patients with hormone receptor-positive tumors, 5-year DFS rate was 99% (95% CI 96% to 100%) in the HER2-negative group as compared with 92% (95% CI 86% to 99%) in the HER2-positive group (HR 5.2, P = 0.04). In patients with hormone receptor-negative tumors, 5-year DFS was 92% (95% CI 84% to 100%) in the HER2-negative group as compared with 91% (95% CI 84% to 99%) in the HER2-positive group. Overall, in hormone receptor-positive and -negative patients,
the HR associated with HER2 overexpression was 2.4 (95% CI 0.9–6.5, \( P = 0.09 \)). Survival of patients with HER2-positive pT1a,bpN0M0 tumors was similar irrespective of the hormone receptor status (\( P = 0.93 \)). None of the patients received adjuvant trastuzumab. In patients with hormone receptor-negative tumors, adjuvant chemotherapy was more frequently given in HER2-negative as compared with HER2-positive patients (66% versus 42%). In the hormone receptor-positive subset, more patients with HER2-negative disease had endocrine treatment alone as compared with the HER2-positive patients (93% versus 65%). In the same hormone receptor-positive patients, combined endocrine treatment and chemotherapy was more frequently given in HER2-positive as compared with HER2-negative patients (24% versus 1%). Thus, endocrine treatment was given in 89% of HER2-positive and in 94% of HER2-negative cases [16]. Finally, a Korean group investigated risk factors for development of metastases in patients with small invasive breast cancer [17]. From 1994 to 2004, 370 node-negative pT1a,bpN0 tumors were identified from 4036 patients who received breast surgery at their institution. The median follow-up was 61 months. Cox regression analysis identified HER2 positivity (HR 5.7, \( P = 0.045 \)) and a triple-negative status (HR 6.0, \( P = 0.049 \)) as independent predictors for DRFS [17].

In summary, 6%–10% of the small node-negative tumors are HER2 positive, and there is increasing evidence from several retrospective studies for an inferior outcome in these patients [18], with recurrence rates of up to 30% after 5–10 years (Table 1). The referred studies, however, have limitations: the analyses were of retrospective nature, the number of HER2-positive tumors and events were small; there were different end points, follow-up times and proportions of patients receiving adjuvant therapy and not all results are available as full paper. Nevertheless, most of the studies are consistent in that they support HER2 status as an important prognostic factors in patients with small HER2-positive tumors. For decision making, it is critical that the HER2 status is correctly identified in the individual patient. The clinician must have absolute confidence in the adequate methodology and interpretation of the pathology results, best by using international recommendations [19] and by both an internal and external quality assurance program.

### adjuvant systemic treatment of small HER-positive tumors: therapeutic options and available evidence

Five of six large clinical studies in patients with HER2-positive tumors showed a consistent reduction in relapse of ~50% when trastuzumab was given as compared with observation [2–9] (Table 2). These studies included patients with node-negative

### Table 2. Overview of the five large trials on the benefit of adjuvant trastuzumab in HER2+ breast cancer; HRs given for the additional benefit of adjuvant trastuzumab compared with no such treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>N</th>
<th>ER and/or PgR+ No.</th>
<th>Node negative No.</th>
<th>pT1 tumors No.</th>
<th>HR for DFS (95% CI)</th>
<th>HR for OAS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA [3, 6, 20]</td>
<td>HER2+ N+</td>
<td>3387</td>
<td>1536</td>
<td>45</td>
<td>1100</td>
<td>32</td>
<td>1347</td>
</tr>
<tr>
<td></td>
<td>HER2+ N– ( \geq ) pT1b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FinHer [2]</td>
<td>N+ N– ( \geq ) 2pT1c PgR&lt;10%</td>
<td>1010</td>
<td>730</td>
<td>72</td>
<td>111</td>
<td>11</td>
<td>441</td>
</tr>
<tr>
<td></td>
<td>HER2+ N+</td>
<td>3969</td>
<td>1748</td>
<td>52</td>
<td>813</td>
<td>6</td>
<td>( 1307 )</td>
</tr>
<tr>
<td></td>
<td>HER2+ N– ( \geq ) 2pT1c ER+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HER2+ N– ( \geq ) 2pT1c ER=</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>HER2+ N+</td>
<td>3222</td>
<td>1740</td>
<td>54</td>
<td>934</td>
<td>29</td>
<td>1289</td>
</tr>
<tr>
<td></td>
<td>HER2+ N– ( \geq ) &amp; risk factors ( \text{e} )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACS-04 [7]</td>
<td>HER2+ N+</td>
<td>3010</td>
<td>528</td>
<td>18</td>
<td>None</td>
<td>32</td>
<td>963</td>
</tr>
</tbody>
</table>

\( \ast \)232 of the patients were HER2+.
\( \ast \)As a proportion of the published 2005 interim analysis [4].
\( \ast \)At least one of the four risk factors: tumor size \( \geq 2 \) cm, ER and/or PgR negative, histological and/or nuclear grade 2–3, age <35 years.
\( \ast \)Comparison of the two trastuzumab-containing arms with the treatment arm without trastuzumab; no 95% CI was given.
\( \ast \)From visual inspection of forest plots.

ACTH, adriamycin, cyclophosphamide, docetaxel (Taxotere \( \text{\textregistered} \)); trastuzumab (Herceptin \( \text{\textregistered} \)); BC, breast cancer; CI, confidence interval; DFS, disease-free survival; ER, estrogen receptor; HR, hazard ratio; N, number of patients; N–, node-negative breast cancer; n.a., not available; OAS, overall survival; PgR, progesterone receptor expression; pT1, tumor with 0–2 cm diameter; RFS, recurrence-free survival; TCH, docetaxel (Taxotere \( \text{\textregistered} \)), carboplatin, trastuzumab (Herceptin \( \text{\textregistered} \)).
tumors of any size or node-negative tumors >1 cm of size, while no direct evidence is available from the large adjuvant studies for the use of trastuzumab in small node-negative tumors. Only the FinHer trial included small node-negative tumors, but the small number of HER2-positive tumors (n=232), non-standard chemotherapy and the short duration of trastuzumab treatment (9 weeks) makes interpretation of the FinHer study difficult [2].

Do we have at least indirect evidence supporting the use of adjuvant treatment in small HER2-positive tumors? Both the HERA and the BCIRG 006 trial included a substantial number of node-negative pT1c tumors, and these lower risk patients had a similar benefit in terms of DFS from adding trastuzumab to chemotherapy as compared with the overall study population [3, 5, 6, 20]. For example, the HR for DFS was 0.53 for patients with node-negative pT1c tumors in the HERA trial, while it was 0.54 for the overall study population. These data strongly suggest that the treatment effect of adjuvant trastuzumab and/or chemotherapy as measured by relative risk reduction is independent of tumor size and nodal status. More data supporting the adjuvant use of trastuzumab in small node-negative HER2-positive breast cancer emerged from two recently reported retrospective investigations. In a French multicenter series from 2000 to 2008, 75 patients with pT1a,bN0 HER2-positive tumors were identified, whereof 33 (44%) received adjuvant chemotherapy, almost all with trastuzumab (n=31) [21]. Adjuvant chemotherapy was more frequently given in patients with hormone receptor-negative tumors, poor differentiation and high mitotic index. Most patients (32 of 39) with hormone receptor-positive tumors received endocrine treatment, but the use of trastuzumab in patients receiving endocrine treatment alone was not reported. With 25 months of median follow-up, there was no invasive recurrence in patients receiving adjuvant trastuzumab, while 3 relapses of 44 patients with no adjuvant trastuzumab or chemotherapy were observed. Another single-institution retrospective study included 495 women with node-negative, HER2-positive tumors ≤2 cm treated in the pre- and post-trastuzumab era [22]. The pre-trastuzumab group included trastuzumab-naïve patients diagnosed from January 2002 to May 2004, while the post-trastuzumab group included trastuzumab-treated patients diagnosed from May 2005 to December 2008. Although patients of both groups had similar age, histology and hormone receptor status, patients in the post-trastuzumab group were more likely to receive adjuvant chemotherapy (97% versus 57%). Events of disease recurrence were significantly more frequent in the pre-trastuzumab group as compared with the post-trastuzumab group (locoregional recurrences 10 versus 0, distant recurrences 9 versus 0, deaths 6 versus 1, respectively) (P=0.007). Both studies support the notion that patients with small node-negative, HER2-positive breast cancer might have a benefit from adjuvant trastuzumab-based therapy. Limitations of these trials include the low number of patients and of events, the retrospective nature and the more frequent use of adjuvant chemotherapy in addition to trastuzumab.

Since the risk of relapse can be substantial in patients with small node-negative tumors (up to 30% at 10 years) and assumed that the relative risk reduction is similar to larger tumors, the absolute benefit might be large enough to consider adjuvant treatment in patients with HER2-positive pT1a,bN0M0 tumors even in the absence of direct evidence. In concordance with the current National Comprehensive Cancer Network (NCCN) guidelines [23], Winer and Burstein [24] recommend physicians to consider trastuzumab-based therapy in patients with HER2-positive tumors pT1bN0 and in particular in the hormone receptor-negative subset. Similar recommendations confined to pT1b tumors were made by the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) in their recently updated treatment guidelines [25]. We share these recommendations in part, even though tumor size may not be the best parameter to decide who should receive adjuvant treatment in this special population. Unfortunately, the risk estimation for tumors <1 cm is not very well characterized. In a Surveillance, Epidemiology and End Results registry-based analysis from Hanrahan et al. [26], 51 246 patients with newly diagnosed pT1a,bN0M0 breast cancer from 1988 to 2001 were identified, and the hazards for dying from breast cancer or competing causes were estimated. The median follow-up was 64 months and median age at diagnosis was 65 years. The 10-year probability of all-cause mortality was 24%, while breast cancer-specific mortality (BCSM) was 4%. Although smaller tumor size was associated with all-cause mortality, BCSM was similar between pT1a and pT1b tumors [26]. In the series from MD Anderson [14] and EIO [16], 44% (n=43) and 57% (n=85) of the patients had HER2-positive tumors ≤5 mm, respectively. In both series, the clinical outcome was similar in patients with pT1a and pT1b tumors. Even in all HER2-positive and HER2-negative tumors from the MD Anderson series (n=965), 5-year DFS was identical with pT1a and pT1b tumors (92% for both groups, without adjuvant chemotherapy and trastuzumab) [14]. Similar results were published by Colleoni et al. [27] in their retrospective analysis, with a similar 4-year DFS in pT1a (n=76, 97%) and pT1b tumors (n=325, 97.6%). The most significant prognostic factor for 4-year DFS in this low-risk population was the proliferation index as measured by Ki-67, with a HR of 12.9 for patients with a high Ki-67 (≥20%) as compared with patients with a low Ki-67 tumor index (<20%). These data are supported by an investigation of 852 node-negative patients with pT1 tumors in a Finish population [11]. In this study, 9-year DDFS was significantly inferior in patients with high (>20%) compared with low Ki-67 (97% versus 90%). Another parameter to better define the risk of relapse in small HER2-positive tumors may be the hormone receptor expression. However, in most investigations, hormone receptor status was without any influence on the risk of relapse in HER2-positive tumors [11, 14, 15]. In contrast, a reduced DFS in patients with HER2-overexpressing tumors was mainly found in the group of ER-positive patients in the EIO series (HR 5.2 versus HR 2.4 for the whole population) [16]. Interestingly, high proliferation status (≥20% Ki-67) (65% versus 17%) and grade 3 histology (35% versus 6%), but not vascular invasion, were significantly overrepresented in HER2-positive, hormone receptor-positive tumors as compared with HER2-positive, hormone receptor-negative tumors. Conversely to the EIO series, HER2 overexpression in the British Columbia series was only of negative clinical value in patients with ER-negative tumors [13].
summary and conclusions

Approximately 6%–10% of small node-negative tumors are HER2 positive, and there is fair evidence for an increased risk of relapse and decreased survival in these patients (Table 1). However, there are no data directly supporting the use of adjuvant treatment including trastuzumab in this patient population. Subgroup analyses from adjuvant trastuzumab trials show that patients with node-negative pT1c tumors derive the same benefit from adjuvant chemotherapy and trastuzumab as compared with patients with higher risk tumors. Furthermore, two retrospective investigations suggest that patients with small node-negative HER2-positive disease may derive clinically relevant benefit from adjuvant trastuzumab-based therapy. As the risk of relapse may be substantial even in small node-negative tumors, and assumed that the relative risk reduction is similar to larger tumors, the absolute benefit should be large enough to consider adjuvant treatment in these patients. However, it is still unclear how to individualize adjuvant treatment, and which type of adjuvant treatment best fits specified patient subgroups. NCCN and AGO guidelines recommend to consider treatment in HER2-positive pT1b/pN0 tumors [23, 25]. Available data do not clearly show a substantial difference in the risk of relapse between pT1a and pT1b HER2-positive tumors. Current data rather suggest tumor biology (proliferation and grade) than shear tumor size to be a more relevant predictor for the risk assessment in these small HER2-positive tumors. The authors suggest that these factors should be included in addition to tumor size in decision making and that adjuvant treatment may also be considered in patients with HER2-positive tumors <6 mm when factors such as increased Ki-67 and/or poor nuclear grade suggest aggressive tumor biology. The value of the hormone receptor status is still controversial and not very helpful since in most of the studies the hormone receptor status was without any influence on the risk of relapse in small HER2-positive tumors. Individual adjuvant treatment must weigh the benefits and risks of the treatment with the risk of relapse and death from breast cancer. The less reliable data we have, the more difficult is the choice of individual treatment. In addition to decide who should be treated, the optimal adjuvant treatment in small HER2-positive tumors is still an open question. Short-term treatment with chemotherapy and trastuzumab has been shown to be effective in reducing the risk of recurrence in HER2-positive breast cancer in the FinHER trial. These less intensive regimens with less toxicity (including little cardiac toxicity) and good tolerability might prove to be adequate for patients with small HER2-positive, node-negative tumors. Furthermore, the addition of trastuzumab to adjuvant endocrine treatment without chemotherapy in small HER2-positive, estrogen receptor-positive tumors is equally controversial as is the addition of chemotherapy to endocrine therapy plus trastuzumab. Data from the metastatic setting suggest endocrine treatment in combination with anti-HER2 targeted treatment to be superior to endocrine therapy alone [28–30]. However, data in the adjuvant setting are lacking. Still for about half of the panelists at the St. Gallen Consensus Conference 2009, this combination was a reasonable option for patients with HER2 and hormone receptor-positive node-negative tumors [31]. Although the proportion of HER2 positivity is lower in small tumors, the absolute increase of lower stage tumors by widespread screening urges for further evaluation in these patients. Future studies with prospective biomarker analysis or gene profiling may better define which patients are at increased risk of relapse and which groups of patients benefit the most from adjuvant systemic treatment. However, the conduct of a randomized clinical trial in this niche population is extremely challenging and might not be realized. Still, patients with small HER-positive, node-negative breast tumors are included into two ongoing trials. The first is a phase two open-label trial investigating the outcome of patients with HER2-positive, node-negative tumors and a tumor size <3 cm. Patients will receive paclitaxel and trastuzumab for 12 weeks followed by trastuzumab maintenance for 40 weeks (NCT00542451). Furthermore, the BETH trial (NSABP-B44, NCT00625898) is a multicenter, randomized, phase 3, four-arm open-label trial recruiting node-negative patients having at least one of the following high-risk features: tumor size ≥2 cm, hormone receptor-negative status, high grade and age <35 years. Patients in this study will be randomized to two different chemotherapy regimens plus trastuzumab with or without bevacizumab. The results of these trials will hopefully help us to optimize treatment decisions in small HER2-positive node-negative breast tumors.

disclosure

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