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ORIGINAL PAPER

# Effectiveness of neoadjuvant trastuzumab and chemotherapy in HER2-overexpressing breast cancer

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**Abstract**
*Purpose* Trastuzumab and chemotherapy is the current standard of care in HER2+ early or locally advanced breast cancer, but there are scanty literature data of its real world effectiveness.
*Methods* We retrospectively reviewed 205 patients with HER2+ breast cancer diagnosed in 10 Italian Medical Oncology Units between July 2003 and October 2011. All patients received neoadjuvant systemic therapy (NST) with trastuzumab in association with chemotherapy. Many different chemotherapy regimens were used, even if 90 % of patients received schemes including anthracyclines and 99 % received taxanes. NST was administered for more than 21 weeks (median: 24) in 130/205 (63.4 %) patients, while trastuzumab was given for more than 12 weeks (median: 12 weeks) in 101/205 (49.3 %) patients. pCR/0 was defined as ypT0+ypN0, and pCR/is as ypT0/is+ypN0.
*Results* pCR/0 was obtained in 24.8 % and pCR/is in 46.8 % of the patients. At multivariate logistic regression, nonluminal/HER2+ tumors ($P < 0.0001$) and more than 12 weeks of neoadjuvant trastuzumab treatment ($P = 0.03$) were independent predictors of pCR/0. Median disease-free survival (DFS) and cancer-specific survival (CSS) have not been reached at the time of analysis.

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At multivariate analysis, nonluminal/HER2+ subclass (DFS: $P = 0.01$ and CSS: $P = 0.01$) and pathological stage II–III at surgery (DFS: $P < 0.0001$ and CSS: $P = 0.001$) were the only variables significantly associated with a worse long-term outcome.

*Conclusions* Our data set the relevance of molecular subclasses and residual tumor burden after neoadjuvant as the most relevant prognostic factors for survival in this cohort of patients.

**Keywords** Breast cancer · Pathological complete response · HER2 · Neoadjuvant · Trastuzumab · Survival

## Introduction

Preoperative or neoadjuvant systemic therapy (NST) for early or locally advanced breast cancer (LABC) is widely used to downstage the primary tumor, thus allowing a higher rate of conservative surgery (van der Hage et al. 2001; Semiglazov et al. 2011; Schott and Hayes 2012), with the same survival benefits as postoperative adjuvant chemotherapy (Bear et al. 2006; van der Hage et al. 2001; Fisher et al. 1997, 1998; Mauri et al. 2005). The human epidermal growth factor receptor 2 (HER2) oncogene is one of the most relevant prognostic and predictive factors for breast cancer patients. HER2 overexpression, which occurs in ~20 % of all breast cancers, has been associated with a poor prognosis both in the early and metastatic setting (Hudis 2007; Ross et al. 2009). However, HER2-positive (HER2+) tumors are highly chemo-sensitive (e.g., to anthracyclines and taxanes) and responsive to the humanized anti-HER2 monoclonal antibody trastuzumab (Herceptin®) (Brufsky 2010; Mariani et al. 2009). Adjuvant chemotherapy plus 52 weeks of trastuzumab is the current standard regimen for HER2+ early breast cancer (Costa et al. 2010; Garnock-Jones et al. 2010; Gianni et al. 2011). Trastuzumab in association with chemotherapy as NST, for early or locally advanced HER2+ breast cancer, has been extensively investigated in phase II–III clinical trials in the last few years (Anton et al. 2011; Burstein et al. 2003; Coudert et al. 2007; Dawood et al. 2007; Gianni et al. 2010; Penault-Llorca et al. 2007; Petrelli et al. 2011; Pierga et al. 2010; Robidoux et al. 2010; Ruiz et al. 2008; Sanchez-Munoz et al. 2010; Sikov et al. 2009; Untch et al. 2010, 2012; Wildiers et al. 2011; Buzdar et al. 2005, 2007; Horiguchi et al. 2009; von Minckwitz et al. 2010; Valachis et al. 2011). A recent systematic review shows that the addition of trastuzumab to chemotherapy has allowed to obtain rates of pathological complete response (pCR) significantly higher than chemotherapy alone (38 vs 21 %; $P$ value <0.001) (Valachis et al. 2011), but a wide variability is observed in clinical trials, ranging from 12 to 67 % (Burstein et al. 2003; Valachis et al. 2011; Buzdar et al. 2005; Harris et al. 2007; Hurley et al. 2006).

Achievement of pCR after NST has been shown to be a good surrogate marker for superior long-term outcome, in terms of disease-free survival (DFS) and possibly overall survival (OS) (Fisher et al. 1998; Symmans et al. 2007; Mazouni et al. 2007; Kaufmann et al. 2006). However, this predictive potential of pCR has been recently questioned by various authors, particularly in relation to the molecular subclasses of breast cancer (Goldhirsch et al. 2011). In fact, patients with luminal A [steroid hormone receptors positive, HER2 negative, low proliferative activity] breast cancer usually show a very low rate of pCR, but their prognosis remains good even when no pCR is achieved (Angelucci et al. 2012; Colleoni et al. 2009; Huober et al. 2010; Precht et al. 2010; Straver et al. 2010; Kim et al. 2010; von Minckwitz et al. 2012). It has been recently reported that pCR is not predictive of survival also in luminal B/HER2+ tumors (steroid hormone receptors positive, HER2+) even when neoadjuvant trastuzumab is administered (von Minckwitz et al. 2012). Moreover, there

**Table 1** Neoadjuvant trastuzumab and chemotherapy in 205 patients with operable or locally advanced HER2-positive breast cancer

| Regimens | *N* (%) |
|---|---|
| Trastuzumab concomitant to taxanes | 123 (60.0) |
| After anthra-based regimens | |
| EC/FEC → Trastuzumab + taxanes | 65 (31.7) |
| EC→ Trastuzumab + docetaxel + carboplatin or capecitabine | 35 (17.1) |
| TEC → Trastuzumab + paclitaxel | 2 (0.1) |
| NPLDoxo + docetaxel→ Trastuzumab + docetaxel | 1 (0.5) |
| Before anthra-based regimens | |
| Trastuzumab + paclitaxel → EC | 2 (0.10) |
| Nonanthra-based regimens | |
| Trastuzumab + taxanes | 14 (6.9) |
| MTX + docetaxel → Trastuzumab + docetaxel | 3 (1.5) |
| Trastuzumab + docetaxel + carboplatin | 1 (0.5) |
| Trastuzumab concomitant to anthracyclines and taxanes | 77 (37.57) |
| Trastuzumab + taxanes → Trastuzumab + FEC or EC | 67 (32.7) |
| Trastuzumab + NPLDoxo + CTX→ Trastuzumab + paclitaxel + carboplatin | 5 (2.4) |
| Trastuzumab + FEC or E → Trastuzumab + taxanes | 5 (2.4) |
| Trastuzumab concomitant to other schemes | 5 (2.43) |

*EC* Epirubicin and cyclophosphamide, *FEC* fluorouracil, epirubicin and cyclophosphamide, *Taxanes* paclitaxel or docetaxel, *TEC* docetaxel, epirubicin and cyclophosphamide, *NPLDoxo* nonpegylated liposomal doxorubicin, *MTX* methotrexate, *CTX* cyclophosphamide, *E* epirubicin

is still no general consensus regarding the definition of pCR, main issues being related to whether or not it should include the presence of noninvasive cancer (von Minckwitz et al. 2010, 2012; Ogston et al. 2003; Chevallier et al. 1993; Sataloff et al. 1995; Green et al. 2005).

The reported high variability of pCR rates in response to neoadjuvant trastuzumab treatment, together with scanty literature data in current clinical practice (Chumsri et al. 2010; Shimizu et al. 2009; Wang et al. 2010; Horiguchi et al. 2011), prompted us to investigate whether the effectiveness of neoadjuvant trastuzumab in association with chemotherapy in 'real world' treatment of HER2+ breast cancer patients is comparable to that observed in randomized controlled trials (RCTs).

## Methods

Two hundred and five consecutive patients with early or locally advanced, HER2+, breast cancer, diagnosed in 10 Italian Medical Oncology Units between July 2003 and October 2011, were retrospectively reviewed. All patients were initially candidates for mastectomy and treated by NST. Diagnosis of invasive breast cancer was established by core biopsy of the primary tumor. Patients with bilateral breast cancer, more than one primary tumor and metastatic disease, were excluded. All patients received preoperative trastuzumab in association with chemotherapy. Chemotherapy regimens administered with trastuzumab included different schemes of treatment (Table 1). Hematopoietic growth factors were used according to local practice.

Trastuzumab was continued postoperatively to complete 52 weeks of treatment in 195 patients. Among 125 patients with steroid hormone receptor-positive tumors, 56 patients were treated with adjuvant tamoxifen, 55 patients with aromatase inhibitors (anastrozole or letrozole), 2 patients with tamoxifen followed by exemestane, 2 patients with LHRH analog and 11 patients did not receive any adjuvant hormonal therapy. Surgical procedures consisted of mastectomy or breast-conserving surgery (BCS) and axillary lymph node dissection. Radiotherapy was administered to patients who underwent BCS and to patients who underwent mastectomy, but had initial stage cT3–T4, cN2 or cN3 disease. The study was approved by the independent ethics committees of participating institutions.

### Pathological assessments

Immunohistochemical assessment of HER2, ER, PgR was performed on pretreatment biopsies and surgical specimens by pathologists of participating centers. Neoadjuvant trastuzumab has been administered only to patients whose tumors scored 3+ by HercepTest$^{TM}$ (Dako Italia, Milan, Italy) and/or were FISH, CISH or SISH positive for HER2 gene amplification. Steroid hormone receptors' status was considered positive if $\geq$1 % of tumor cells stained for ER and/or PgR. Immunohistochemical detection of Ki-67 was performed using the MIB-1 antibody (Dowsett et al. 2011), and the positivity cutoff value was set at 14 % (Goldhirsch et al. 2011). The nuclear grade was assessed according to the Nottingham grading system (Elston and Ellis 1991). The American Joint Committee on Cancer staging system, 7th ed (2010), was used for tumor staging. Locoregional recurrence (LRR) was defined as any histologically proven chest wall recurrence in those patients who underwent mastectomy, any ipsilateral breast recurrence in those achieving breast conservation and any recurrence in the axillary, supraclavicular or internal mammary nodes.

### Data collection

A retrospective review of clinical, pathological and treatment data for all patients was carried out, and data were entered on an anonymized database. The cutoff date for follow-up was set on October 31, 2012. Since patients enrollment started in 2003, complete data information was not available for all 205 patients; thus, denominators may vary throughout the article. Patients were followed up at 6-month intervals over the first 5 years and at 12-month intervals thereafter.

### Study endpoints and statistics

pCR was defined as either the absence of invasive and noninvasive breast cancer in the breast and axillary lymph nodes (ypT0 and ypN0, later on referred to as pCR/0) or the absence of invasive breast cancer in the breast and axillary lymph nodes (ypT0/is and ypN0, later on referred to as pCR/is), and the latter also classified as Stage 0 (Kuerer et al. 1999; Kaufmann et al. 2010). Disease-free survival (DFS) was calculated from the time of breast surgery to the first occurrence of local relapse, distant metastasis or intercurrent deaths without distant recurrence, and cancer-specific survival (CSS) was calculated from the date of surgery to that of death from breast cancer or last follow-up examination. Two patients were reported to die from causes other than breast cancer. Survivors were censored at the date of last contact. The relationships between patients/tumor characteristics and pCR were assessed by Pearson's $\chi^2$ or Fisher's exact test, as appropriate. Univariate models were developed, and all significant univariate predictors were considered for inclusion in multivariate models. The prediction of pCR was evaluated with a stepwise multivariate logistic regression model. DFS and CSS were estimated using Kaplan–Meier analysis; the log-rank test and Tarone–Ware test for trend were used to assess

**Table 2** Association of clinical characteristics and pCR in univariate analysis

| | *N* (%) | pCR/0 (*ypT0, ypN0*) *N* (%) | *P* value | pCR/is (*ypT0/is, ypN0*) *N* (%) | *P* value |
|---|---|---|---|---|---|
| Histologic type | | | | | |
| Ductal | 179 (87.3) | 44 (24.6) | 0.76 | 86 (48.0) | 0.36 |
| Lobular | 12 (5.9) | 4 (33.3) | | 6 (50.0) | |
| Others | 14 (6.8) | 3 (21.4) | | 4 (28.6) | |
| Clinical T | | | | | |
| $T_1$–$T_2$ | 119 (58.0) | 34 (28.6) | 0.84 | 61 (51.3) | 0.37 |
| $T_3$–$T_4$ | 59 (28.8) | 16 (27.1) | | 26 (44.1) | |
| Unknown^ | 27 (13.2) | | | | |
| Grade | | | | | |
| 1–2 | 70 (34.2) | 22 (31.4) | 0.83 | 34 (48.6) | 0.74 |
| 3 | 74 (36.0) | 22 (29.7) | | 38 (51.3) | |
| Unknown^ | 61 (29.8) | | | | |
| Ki-67 | | | | | |
| <14 % | 26 (12.7) | 3 (11.5) | 0.05 | 12 (46.2) | 0.75 |
| ≥14 % | 127 (62.0) | 38 (29.9) | | 63 (49.6) | |
| Unknown^ | 52 (25.4) | | | | |
| Molecular subclasses | | | | | |
| HER2+, ER+ and/or PgR+° | 125 (61.0) | 20 (16.0) | 0.001 | 51 (41.1) | 0.05 |
| HER2+, ER−, PgR−* | 80 (39.0) | 30 (37.5) | | 44 (55.0) | |
| NST duration | | | | | |
| ≤21 weeks | 75 (36.6) | 14 (18.7) | 0.12 | 35 (46.7) | 0.97 |
| >21 weeks | 130 (63.4) | 37 (28.5) | | 61 (46.9) | |
| Trastuzumab duration in NST | | | | | |
| ≤12 weeks | 104 (50.8) | 20 (19.2) | 0.06 | 45 (43.3) | 0.30 |
| >12 weeks | 101 (49.3) | 31 (30.7) | | 51 (50.5) | |

*HER2* Human epidermal growth factor type 2, *ER* estrogen receptors, *PgR* progesteron receptors

^ Unknown were not included in univariate analysis,
° Luminal B/HER2+,
* nonluminal/HER2+

differences between subgroups (Massarweh et al. 2006; Tarone 1975; Kaplan and Meier 1958). The hazard ratio (HR) and the 95 % confidence intervals (95 % CI) were estimated for each variable. A multivariate Cox proportional hazards model was carried out to assess the relative influence of prognostic factors on survival. Enter and remove limits were $P = 0.10$ and $P = 0.15$, respectively. The assessment of interactions between significant investigation variables was taken into account when developing the multivariate model. All of the tests were two-sided, and $P \leq 0.05$ was considered significant. All statistical analyses were performed using the SPSS Statistic software 19 (SPSS Inc., Chicago, III).

## Results

### Patients' characteristics and response to NST

From July 2003 to April 2012, 205 patients with HER2+ early or LABC, candidates for mastectomy, were treated with neoadjuvant trastuzumab in association with different schemes of chemotherapy in 10 Italian Medical Oncology Units. Median age at diagnosis was 48.1 years (range 25–77 years) with 19 (9.3 %) patients being younger than 40 years and 11 (5.4 %) older than 65 years. The associations of baseline clinical characteristics and treatment parameters with pCR/0 and pCR/is are reported in univariate analysis in Table 2. Eighty-seven percent of the tumors (179/205) were invasive ductal carcinomas with a high proliferative activity (62.0 % with Ki-67 ≥14 %). Most tumors (58.0 %) were clinical $T_1$–$T_2$; tumor grade was 1–2 in 70 (34.2 %) and grade 3 in 74 (36.0 %) tumors. Luminal B/HER2+ (HER2+, ER+ and/or PgR+) molecular subclass was represented in 61.0 % (125/205) of cases and nonluminal/HER2+ subclass in 39.0 % (80/205).

Patients were treated with many different chemotherapy regimens. However, 90 % (186/205) of patients received schemes including anthracyclines and all but 3 patients (99 %) received taxanes, either paclitaxel or docetaxel (Table 1). NST was administered for more than 21 weeks (median: 24, range 9–30 weeks) in 130/205 (63.4 %)

**Table 3** Predictive factors of pCR/0 according to the multivariate logistic regression model

| Variables | pCR/0 | |
|---|---|---|
| | OR (95% CI) | *P* value |
| Molecular subclasses | | |
| HER2+, ER−, PgR−* versus HER2+, ER+ and/or PgR+° | 4.03 (1.85–8.74) | <0.0001 |
| Trastuzumab duration in NST | | |
| >12 weeks versus ≤12 weeks | 2.40 (1.10–5.22) | 0.03 |

*HER2* Human epidermal growth factor type 2, *ER* estrogen receptors, *PgR* progesteron receptors, *OR* odds ratio, *CI* confidence intervals

° Luminal B/HER2+, * nonluminal/HER2+

patients, while trastuzumab was given for more than 12 weeks (median: 12 weeks; range 5–27 weeks) in 101/205 (49.3 %) patients. pCR/0 was obtained in 51/205 (24.8 %) patients and pCR/is in 96/205 (46.8 %) patients. As shown in Table 2, the absence of steroid hormone receptors was highly predictive of pCR/0 ($P = 0.001$), less of pCR/is ($P = 0.05$). There was a trend toward higher rates of pCR/0 for tumors with a high proliferative index ($P = 0.05$) and for a longer duration of neoadjuvant trastuzumab therapy ($P = 0.06$). At multivariate logistic regression, nonluminal/HER2+ tumors (OR 4.03; 95 % CI 1.85–8.74; $P < 0.0001$) and treatment with trastuzumab for more than 12 weeks (OR 2.49; 95 % CI 1.10–5.22; $P = 0.03$) were independent predictors of pCR/0 (Table 3). No other predictive factors were identified either for pCR/0 or pCR/is.

### Patients' characteristics and survival

Breast conservative surgery was performed in 97/205 (47.3 %) patients, and radiotherapy was given to 45 of 108 (41.7 %) patients who underwent mastectomy (Table 4). All patients had axillary lymph node dissection. Residual invasive tumors in the breast were detected in 101/205 (49.3 %) patients, residual noninvasive tumor in 45/205 (21.9 %) patients and positive axillary nodes in 53/205 (25.9 %) patients. Pathological stage 0 (ypT0, ypT0/is, ypN0) was assessed in 96/205 (46.8 %), stage I in 35/205 (17.1 %) and stage II–III in 74/205 (36.1 %) patients. Adjuvant chemotherapy was administered to 14/205 (6.8 %) patients and adjuvant hormonal therapy to 114/125 (91.2 %) patients with steroid hormone receptors-positive tumors. In 195/205 (95.1 %) patients, trastuzumab was continued postoperatively to complete 52 weeks of treatment.

The median follow-up period was 32 months (range 2–106 months). Median DFS and CSS have not been reached at the time of analysis. The mean DFS time was 79 months (95 % CI 70–89), and the mean OS was 94 (95 % CI 89–100) months. During follow-up, 15/205 (7.3 %) patients had local relapse, 30/205 (14.6 %) developed distant metastases (10 of them in the central nervous system) and 18/205 (8.8 %) died from breast cancer. The 5-year estimates were 73.3 % for DFS and 82.8 % for CSS in the all patients' population. For subsequent survival analyses, we show only data using pCR/is since (1) results were superimposable to those obtained with pCR/0 (data not shown), and (2) pCR/is is included in pathological stage 0 definition (ypT0, ypT0/is, ypN0). At Kaplan–Meier analysis, pCR/is was not found to be a predictive factor for DFS and CSS (data not shown). However, in the molecular subclass of nonluminal/HER2+ (HER2+, ER−, PgR−) pCR/is was predictive of better outcome in terms of DFS ($P = 0.04$; HR = 0.38, 95 % CI 0.15–0.96) with a trend toward significance for CSS ($P = 0.25$; HR = 0.48, 95 % CI 0.14–1.66, Fig. 1). Patients with nonluminal/HER2+ tumors (HER2+, ER−, PgR−) showed a trend toward a worse DFS ($P = 0.06$; HR = 1.82, 95 % CI 0.96–3.45) and CSS ($P = 0.053$; HR = 2.55, 95 % CI 0.99–6.58, Fig. 2) compared to those with luminal B/HER2+. Moreover, patients with pathological stage II–III at surgery were more likely to have a shorter DFS ($P = 0.001$; HR = 2.92, 95 % CI 1.53–5.56) and to die from breast cancer ($P = 0.01$; HR = 3.52, 95 % CI 1.36–9.12, Fig. 3). Type of surgery, residual tumor size, node positivity, pathological stages were also predictive factors of DFS and CSS at univariate analysis (Table 4). At multivariate analysis, the predictive factors of DFS and CSS were the nonluminal/HER2+ molecular subclass (DFS: $P = 0.01$ and CSS: $P = 0.01$) and pathological stage II–III at surgery (DFS: $P < 0.0001$ and CSS: $P = 0.001$) (Table 5).

## Discussion

Nowadays we assist to an increasing debate on the relative value of RCTs in assisting decision making in day-to-day clinical practice, being this the main endpoint of comparative effectiveness research (Lyman and Levine 2012; Korn and Freidlin 2012). Although RCTs remain the gold standard for comparing treatments, patient selection criteria and the lack of flexibility in protocol-specified dose modifications and toxicity management limit the generalizability of the findings to the individual patient (Hahn and Schilsky 2012). The major questions are whether results of RCTs can be applied to 'real world' patients (sometimes with medical co-morbidities or borderline organ function), whether they are also reliably for subsets of patients with different clinical characteristics and whether patients non-enrolled in RCTs have a worst outcome than randomized

**Table 4** Clinical characteristics of patients and DFS and CSS in univariate analysis

| | *N* (%) | 5-yr DFS % | *P* value″ | 5-yr CSS % | *P* value″ |
|---|---|---|---|---|---|
| Molecular subclasses at diagnosis | | | | | |
| HER2+, ER+ and/or PgR+° | 125 (61.0) | 78.4 | 0.06 | 89.2 | 0.04 |
| HER2+, ER−, PgR− * | 80 (39.0) | 66.0 | 0.05 | 73.1 | 0.06 |
| pCR/0 (ypT0, ypN0) | | | | | |
| Yes | 51 (24.8) | 86.3 | 0.11 | 83.5 | 0.71 |
| No | 154 (75.2) | 68.7 | 0.18 | 82.9 | 0.55 |
| pCR/is (ypT0/is, ypN0) | | | | | |
| Yes | 96 (46.8) | 82.3 | 0.12 | 86.3 | 0.18 |
| No | 109 (53.2) | 65.7 | 0.12 | 79.7 | 0.10 |
| Type of surgery | | | | | |
| Breast conservative surgery | 97 (47.3) | 77.9 | 0.08 | 86.0 | 0.03 |
| Mastectomy | 108 (52.7) | 67.9 | 0.05 | 76.9 | 0.01 |
| Radiotherapy | | | | | |
| Yes | 142 (69.3) | 79.5 | 0.96 | 83.6 | 0.32 |
| No | 63 (30.8) | 72.0 | 0.73 | 83.0 | 0.26 |
| Mastectomy | | | | | |
| With radiotherapy | 45 (41.7) | 52.9 | 0.29 | 77.5 | 0.68 |
| Without radiotherapy | 63 (58.3) | 77.4 | 0.48 | 78.7 | 0.66 |
| Residual tumor size | | | | | |
| ypT0/is | 104 (50.7) | 79.1 | 0.04 | 84.7 | 0.02 |
| ypT1 | 55 (26.9) | 75.8 | 0.03 | 86.6 | 0.006 |
| ypT2 | 37 (18.0) | 61.2 | | 63.5 | |
| ypT3 | 9 (4.4) | 55.6 | | 65.6 | |
| Node involvement | | | | | |
| ypN0 | 152 (74.1) | 78.0 | 0.02 | 86.5 | 0.05 |
| ypN+ | 53 (25.9) | 58.9 | 0.02 | 66.7 | 0.05 |
| Pathological stage | | | | | |
| 0^ | 96 (46.8) | 82.3 | 0.005 | 83.5 | 0.02 |
| I | 35 (17.1) | 84.4 | 0.006 | 100.0 | 0.02 |
| II | 67 (31.7) | 54.5 | | 64.3 | |
| III | 7 (3.4) | 71.4 | | 75.0 | |
| Adjuvant chemotherapy | | | | | |
| Nil | 191(93.2) | 76.4 | 0.63 | 81.3 | 0.64 |
| Yes | 14 (6.8) | 43.6 | 0.85 | 85.7 | 0.54 |
| Adjuvant Trastuzumab | | | | | |
| Nil | 10 (4.9) | 56.2 | 0.64 | 87.5 | 0.91 |
| Up to 52 weeks of treatment | 195 (95.1) | 74.7 | 0.64 | 70.9 | 0.81 |
| Adjuvant hormonal therapy | | | | | |
| Nil | 91 (44.4) | 68.1 | 0.14 | 75.0 | 0.12 |
| Yes | 114 (55.6) | 77.8 | 0.09 | 86.9 | 0.14 |

*HER2* Human epidermal growth factor type 2, *ER* estrogen receptors, *PgR* progesteron receptors

° Luminal B/HER2+, * nonluminal/HER2+, ^ ypT0/is, ypN0, ″ the first *P* value is determined by log-rank test and the second one by Tarone-Ware test

patients (Korn and Freidlin 2012; Braunholtz et al. 2001; Peppercorn et al. 2004; Hannouf et al. 2012; Engstrom et al. 2012; Tanai et al. 2011). From this point of view, observational retrospective studies are considered alternative good sources of information on the effectiveness of treatments used according to patient and tumor characteristics (Korn and Freidlin 2012; Lyman and Levine 2012).

In the last few years, several phase III RCTs have demonstrated the efficacy of neoadjuvant trastuzumab in association with chemotherapy in HER2+ early or LABC (Gianni et al. 2011; Burstein et al. 2003; Gianni et al. 2010; Untch et al. 2010, 2012; von Minckwitz et al. 2010; Buzdar et al. 2005). A recent meta-analysis of five phase II–III RCTs shows that in the overall population of 515 patients,

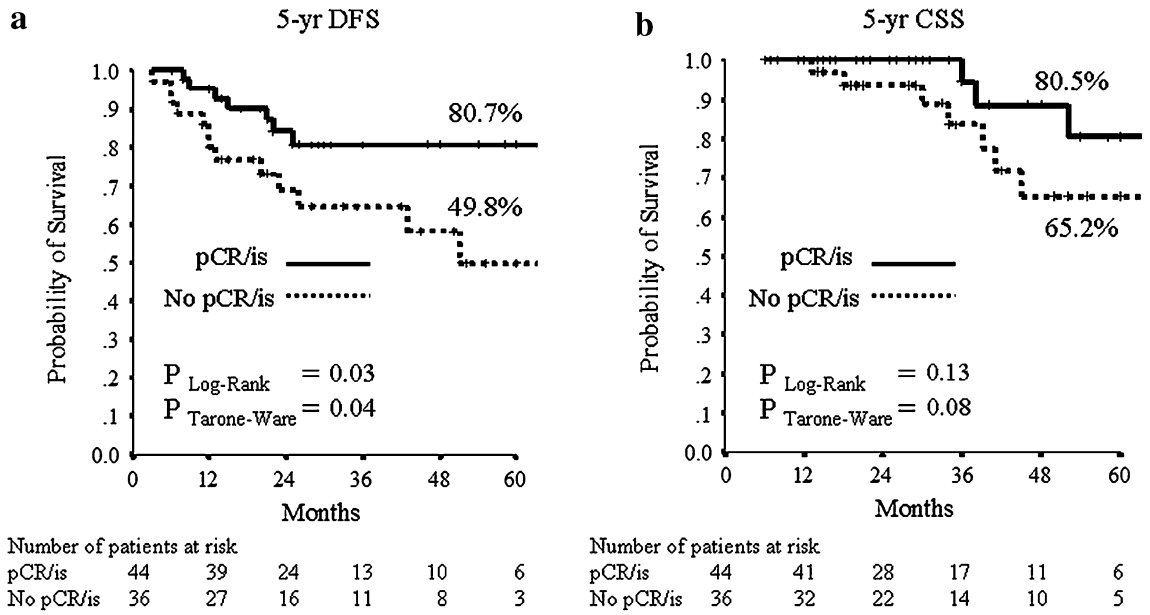


**Fig. 1** **a** 5-years distant DFS and **b** 5-years CSS stratified by pathological complete response (ypT0/is, ypN0: pCR/is) for the nonluminal/HER2+ subclass, excluding patients with luminal B/HER2+ tumors

the absolute pCR rate is 38 % in the trastuzumab arm, with no data on survival (Valachis et al. 2011).

Here we report the effectiveness of neoadjuvant trastuzumab in association with different chemotherapy regimens, in a heterogeneous series of 205 patients with HER2+ operable breast cancer, treated in 10 Italian Medical Oncology Units. Our results show that (1) pCR/0 is obtained in 24.8 % and pCR/is in 46.8 % of the patients; (2) nonluminal/HER2+ subclass and neoadjuvant trastuzumab treatment for more than 12 weeks are predictive factors of pCR/0; (3) pCR (calculated either including or not residual noninvasive cancer cells) is predictive of DFS and CSS only in the nonluminal/HER2+ subclass; and (4) luminal B/HER2+ tumors and pathological stage 0–I disease at surgery are associated with a better DFS and CSS.

Our overall results deserve some considerations. Here we report that neoadjuvant trastuzumab for more than 12 weeks of treatment is associated with a significantly higher rate of pCR/0 than shorter treatments (OR 2.49; 95 % CI 1.10–5.22; $P = 0.03$). To our knowledge, no RCTs evaluated clinical effectiveness of longer versus shorter neoadjuvant trastuzumab administration, and this

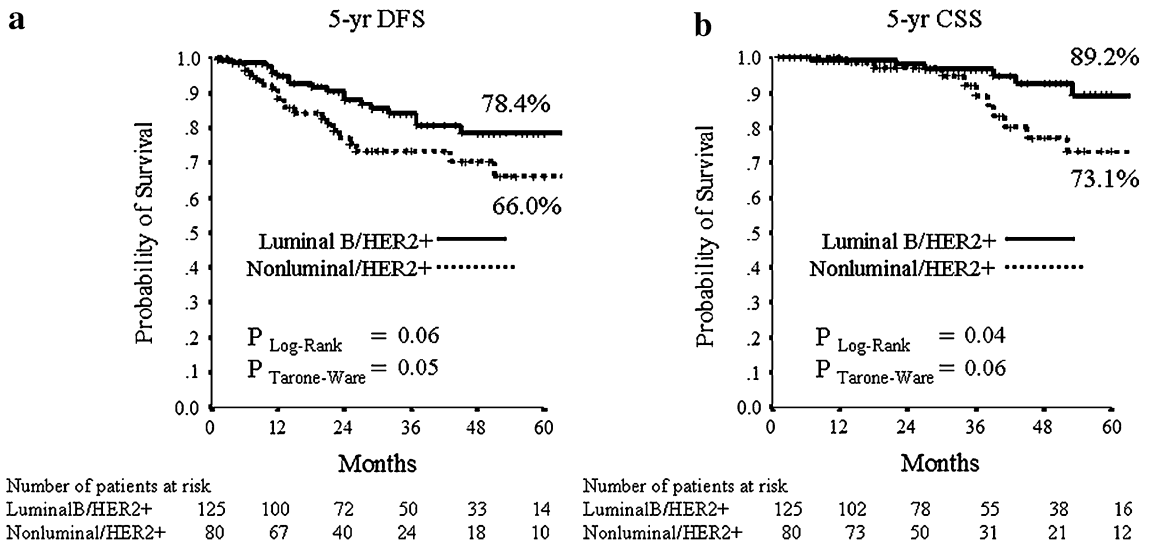


**Fig. 2** **a** 5-years distant DFS and **b** 5-years CSS stratified by molecular subclass

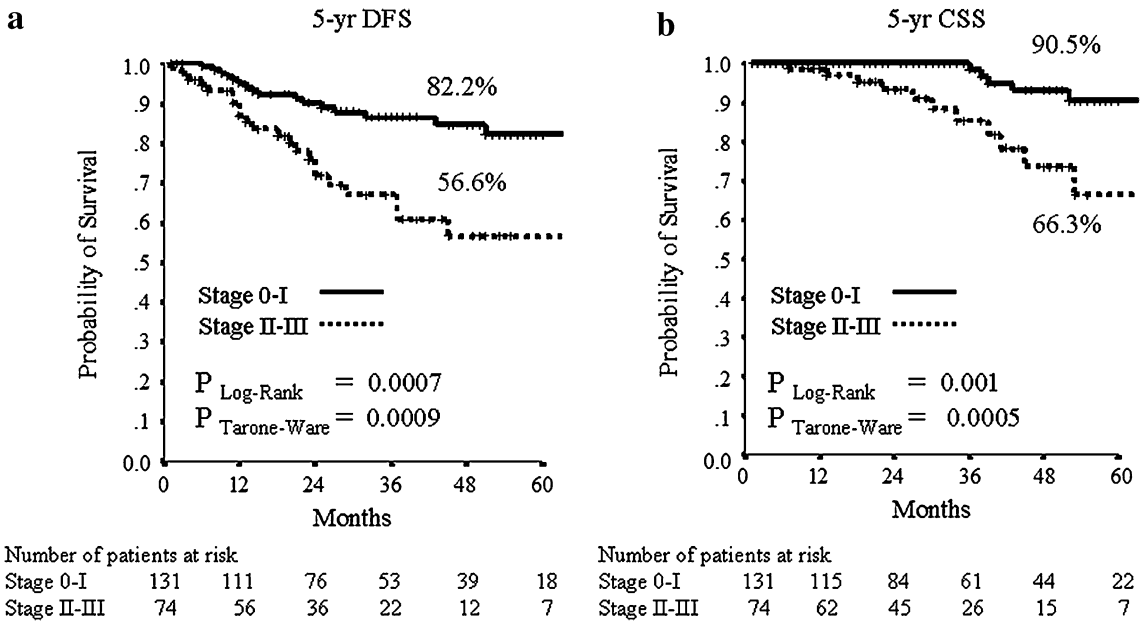


**Fig. 3** **a** 5-years distant DFS and **b** 5-years CSS stratified pathological stage at surgery

**Table 5** Prognostic factors according to the multivariate Cox regression model

| Variables | DFS | | CSS | |
|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Molecular subclasses | | | | |
| HER2+, ER−, PgR−* versus HER2+, ER+ and/or PgR+° | 2.38 (1.24–4.57) | 0.01 | 3.71 (1.32–10.39) | 0.01 |
| Pathological stage | | | | |
| II–III versus 0–I | 3.51 (1.81–6.81) | <0.0001 | 6.36 (2.15–18.74) | 0.001 |

*DFS* Disease-free survival, *CSS*-cancer specific survival, *HER2* human epidermal growth factor type 2, *ER* estrogen receptors, *PgR* progesteron receptors

° Luminal B/HER2+, * nonluminal/HER2+, *HR* hazard ratio, *CI* confidence intervals

issue is object of debate (Untch et al. 2011). A pooled analysis of the German neoadjuvant chemotherapy trials found little evidence that an increasing number of trastuzumab cycles is associated with higher pCR rates in HER2+ patients (von Minckwitz et al. 2011). A retrospective study on neoadjuvant therapy for HER2+ breast cancer reported that patients treated with a regimen in which trastuzumab was administered concurrently with anthracyclines for 24 weeks (trastuzumab and paclitaxel for 12 weeks followed by trastuzumab and FEC for 12 weeks) achieved a higher pCR rate compared to that observed in patients treated with 18 weeks of trastuzumab in association with a nonanthracycline-based regimen, docetaxel and carboplatin (60.6 vs 43.3 %; $P = 0.016$) (Bayraktar et al. 2012). Authors linked the higher pCR rate to the concurrent trastuzumab administration with a sequential regimen of a taxane followed by an anthracycline-containing regimen and not to the longer trastuzumab exposure (Bayraktar et al. 2012). However, in our cohort, over 90 % of patients received schemes of chemotherapy including anthracyclines and almost all received taxanes, though with different sequences and combinations.

The pCR/0 (24.8 %) and pCR/is (46.8 %) rate observed in our series is within the range of the pCR rates reported in the literature (Untch et al. 2012; Valachis et al. 2011; Ismael et al. 2012). Similarly to von Minckwitz and coll. (von Minckwitz et al. 2012), we had a higher rate of pCR/0 and pCR/is in patients with the worst prognostic factors, for example high proliferative activity and nonluminal/HER2+ tumors. Moreover, pCR/0 and pCR/is achieved similar results in terms of DFS and CSS, being both predictive of better outcome only in the molecular subclass of luminal B/HER2+ tumors.

The long-term outcome of patients included in this analysis was significantly affected by steroid hormone

receptors expression and residual tumor burden at surgery. Luminal B/HER2+ molecular subclass was associated with a better outcome, as reported for luminal A, luminal B/HER2-negative and luminal B/HER2+ tumors in other series (Goldhirsch et al. 2011; Angelucci et al. 2012; Houssami et al. 2012; Tran and Bedard 2011). Pathological stage 0–I was also predictive of better outcome in our cohort of patients, in line with data showing that among patients with residual disease, a higher tumor burden at surgery is predictive of a worst outcome (Fisher et al. 1998; Angelucci et al. 2012; Cance et al. 2002; Carey et al. 2005).

The strength of this multicenter retrospective observational study is that it represents data from a cohort of 'real world' individual patients with a wide age range (from 25 to 77 years), treated with neoadjuvant trastuzumab outside of clinical trials in association with different schemes of chemotherapy regimens (Table 1), with different duration of NST (from 9 to 30 weeks), and trastuzumab treatment (from 5 to 27 weeks), in 10 different oncology units with optimal follow-up adherence (no patient lost to follow-up). The main weaknesses are represented (1) by the fact that inclusion/exclusion criteria, therapeutic regimens, dose modifications and toxicity management for neoadjuvant trastuzumab treatment were not defined from a predefined study protocol, thus leaving them to the single oncology unit decision and (2) preoperative complete data information, such as clinical T, grade and Ki-67, were not available for all 205 patients,

In conclusion, this study shows that a longer duration of trastuzumab treatment and the absence of estrogen and/or progesterone receptors are significantly associated with a higher rate of pCR/0. pCR/0 and pCR/is are predictive of a better outcome only in luminal B/HER2+ tumors. High residual tumor burden after NST (i.e., pathological stage II–III at surgery) and the absence of estrogen and/or progesterone receptors are both independent predictors of shorter DFS and CSS.

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