J Cancer Res Clin Oncol
DOI 10.1007/s00432-015-2033-z

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Demographic, tumor and clinical features of clinical trials versus clinical practice patients with HER2-positive early breast cancer: results of a prospective study

Grazia Arpino[1] · Andrea Michelotti[2] · Mauro Truini[3] · Filippo Montemurro[4] · Stefania Russo[5] · Raffaella Palumbo[6] · Claudio Zamagni[7] · Agnese Latorre[8] · Dario Bruzzese[9] · Ferdinando Riccardi[10] · Michelino De Laurentiis[11] · Alessandra Beano[12] · Laura Biganzoli[13] · Alberto Zaniboni[14] · Lucio Laudadio[15] · Maria Malagoli[16] · Domenico Bilancia[17] · Francesco Schettini[1] · Mario Giuliano[1] · Marina Elena Cazzaniga[18] · Sabino De Placido[1]

Received: 13 July 2015 / Accepted: 15 August 2015

Abstract

Background Several randomized clinical trials (RCTs) have demonstrated the efficacy of trastuzumab-based adjuvant therapy in HER2-positive breast cancer (BC). However, RCT patients may not invariably be representative of patients routinely seen in clinical practice (CP). To address this issue, we compared the clinical and tumor features of RCT and CP patients with HER2-positive BC.

Patients and methods From January to December 2012, 650 consecutive patients with HER2-positive early BC, treated in 36 different types of Italian healthcare facilities, were enrolled in this study. Age, treatment, tumor size (T), nodes (N), grade (G), estrogen receptor (ER) and progesterone receptor (PgR) status were prospectively collected in these CP patients. The same data were extracted from the main adjuvant trastuzumab RCTs and pooled using the random-effects model of DerSimonian and Laird. RCT and CP patients were compared by using the Cochran Q statistics.

Results Versus RCT patients, CP patients were more likely to be older than 50 years (65 vs. 49 %; $p < 0.0001$) and to have HR (ER and/or PgR)-positive (72 vs. 54 %; $p < 0.0001$) BC and less likely to have tumor >2 cm ($T \geq 2$ cm 39 vs. 59 %; $p < 0.0001$), positive N (47 vs. 89 %; $p < 0.0001$) and a high G (61 vs. 67 %; $p = 0.0241$). CP patients more frequently received adjuvant endocrine therapy (70 vs. 57 %; $p < 0.0003$) and less frequently adjuvant chemotherapy (97 vs. 99.7 %; $p < 0.0001$).

Conclusions Most tumor and clinical features differed significantly between CP and RCT patients. These data

✉ Grazia Arpino
grazia.arpino@unina.it

1 Department of Clinical Medicine and Surgery, University of Naples Federico II, Via S. Pansini 5, 80131 Naples, Italy

2 Medical Oncology, "Santa Chiara" Hospital, University of Pisa, Pisa, Italy

3 Department of Pathology, National Institute for Cancer Research, Genoa, Italy

4 Investigative Clinical Oncology, Candiolo Cancer Institute, Candiolo, Italy

5 Medical Oncology, University Hospital, Udine, Italy

6 Service of Preventive Oncology, IRCCS Fondazione "Salvatore Maugeri", Pavia, Italy

7 Medical Oncology Unit, "S.Orsola-Malpighi" Hospital, Bologna, Italy

8 National Cancer Institute, Bari, Italy

9 Preventive Medical Sciences, University of Naples "Federico II", Naples, Italy

10 Medical Oncology, "A. Cardarelli" Hospital, Naples, Italy

11 National Cancer Institute Fondazione "G.Pascale", Naples, Italy

12 Presidio Evangelico Valdese-ASL TO1, Area Medica, Turin, Italy

13 Department of Medical Oncology, Hospital of Prato, Istituto Toscano Tumori, Prato, Italy

14 Department of Medical Oncology, Casa di Cura Poliambulanza, Brescia, Italy

15 Medical Oncology, Ospedale F. Renzetti, Lanciano, Italy

16 Oncology, Ospedali Riuniti di Trieste, Trieste, Italy

17 Oncology, "San Carlo" Hospital, Potenza, Italy

18 Medical Oncology, "San Gerardo" Hospital, Monza, Italy

Published online: 25 August 2015

raise concerns about the applicability of RCT results to CP patients.

Keywords Clinical practice · Early breast cancer · HER2 · Adjuvant therapy · Trastuzumab

Abbreviations

RCT	Randomized clinical trials
CT	Clinical trials
HER2	Human epidermal growth factor receptor 2
BC	Breast cancer
CP	Clinical practice
ER	Estrogen receptor
PgR	Progesterone receptor
HR	Hormone receptors
T	Tumor size
N	Nodal status
G	Grading

Introduction

The human epidermal growth factor receptor 2 (HER2) gene is overexpressed/amplified in 10–25 % (Coussens et al. 1985; Slamon et al. 1987, 1989; Perou et al. 2000) of human breast cancers (BCs), and in such cases, it is typically associated with high biological aggressiveness and a poor prognosis (Slamon et al. 1987; Wolff et al. 2007; Curigliano et al. 2009; Gonzalez-Angulo et al. 2009; Chia et al. 2009). The introduction in clinical practice of effective HER2-targeted therapies has dramatically improved the prognosis of patients with HER2-positive disease. Impressive results were obtained in many randomized clinical trials (RCTs) in the adjuvant/neoadjuvant and advanced setting based on the use of trastuzumab, a monoclonal antibody targeted against the external domain of HER2, administered in association with, or sequentially to chemotherapy (Slamon et al. 2011; Joensuu et al. 2006; Spielmann et al. 2009; Piccart-Gebhart et al. 2005; Romond et al. 2005; Cobleigh et al. 1999; Slamon et al. 2001; Vogel et al. 2002; Seidman et al. 2008; Burstein et al. 2007; Robert et al. 2006; Von Minckwitz et al. 2008). More recently, the RCTs CLEOPATRA (Baselga et al. 2012) and EMILIA (Verma et al. 2012), which evaluated the monoclonal antibodies, pertuzumab and T-DM1, marked a positive change in the natural history of metastatic HER2-positive BC. However, RCTs may not be representative of a "real patient population" because patients enrolled in RCTs are usually free from such comorbidities as hematologic, renal or cardiac dysfunctions, and are selected for specific tumor features, such as tumor size and/or nodal status at diagnosis. For example, one of the most important clinical trials with trastuzumab in the adjuvant setting, the HERA trial (Piccart-Gebhart et al. 2005), enrolled only lymph node-positive patients regardless of tumor size, or node-negative patients with tumor size larger than 1 cm. The issue of the applicability of RCT results to routine clinical practice is particularly relevant when a treatment such as trastuzumab is given to almost all patients with HER2-positive early BC (EBC).

In this study, we evaluated differences, in terms of clinical and tumor characteristics and comorbidities, between RCT patients and patients routinely seen in clinical practice not enrolled in clinical trials, to assess whether the populations enrolled in RCTs are sufficiently representative of the general EBC population, and, importantly, to determine whether RCT results are fully translatable into daily clinical practice.

Materials and methods

Study design

This was a prospective multicenter observational study. Thirty-six different types of Italian healthcare facilities, representative of the entire Italian healthcare system, participated in the study. Clinical and demographic patient data were centrally collected from each participant institution in an anonymous online database designed by C.R.T. S.r.l. (Salerno, Italy), accessible only to accredited study participants. Our data were then compared with those obtained from the main adjuvant trastuzumab RCTs, namely FNCLCC-PACS-04, BCIRG-006, FinHER, HERA and NSABP B31-NCCTG N9831. No patient identifiers were provided to the authors. The study design and informed consent were approved by the ethic committees of each participant center (IRB protocol number for Coordinating Center: 144/12). All patients signed an appropriate informed consent concerning aim and design of the study and allowed to publish relevant data in anonymous form.

Population characteristics

A total of 650 consecutive patients with HER2-positive EBC treated at the participant institutions from January to December 2012 were enrolled in the study. Age, menopausal status, treatment information, tumor size (T), axillary nodal status (N), grade (G), histotype, estrogen receptor (ER), progesterone receptor (PgR) and cumulative hormone receptor (HR) status were prospectively collected in clinical practice (CP) patients. Our patients were not enrolled in an RCT not because they failed to meet entry criteria, but simply because no RCT was ongoing in any of the participating centers.

In parallel, the same data were extracted, where possible, from the adjuvant trastuzumab RCTs, FNCLCC-PACS-04, BCIRG-006, FinHER, HERA and NSABP B31-NCCTG

N9831 (total number of patients: 11,414). Tumor grading was not reported in the BCIRG-006 trial, and histologic subtype was reported only in the FinHER and FNCLCC-PACS04 trials. Quantitative data on ER and PgR expression were missing from the FNCLCC-PACS04, BCIRG-006 and HERA trials. In these three trials, data on HR status were reported as ER and/or PgR positivity/negativity; therefore, we considered the cumulative HR status. HER2 positivity was determined locally and defined as immunohistochemical staining intensity of 3+ or 2+ with evidence of gene amplification at fluorescence in situ hybridization. The polyclonal antibody A0485 (Dako, Milan, Italy) was used for HER2 immunostaining. HER2 immunohistochemistry positivity was determined according to the American Society of Clinical Oncology—College of American Pathologists guidelines (Wolff et al. 2007).

Statistical analyses

A meta-analytical approach was undertaken to compare the distribution of the clinical and demographical characteristics of women enrolled in clinical trials and those treated in clinical practice. In particular, the clinical and demographic characteristics extracted from RCTs were initially pooled using the random-effects model of DerSimonian and Laird (1986). In this step, to correct over-dispersion, the raw proportions were converted using the Freeman–Tukey transformation and back-transformed after quantitative data synthesis (Freeman and Tukey 1950; Miller 1978). Although in some cases the degree of heterogeneity, as estimated by the I^2 statistics, was low, we decided to use the random-effect model for all the characteristics because it produced the most conservative estimates. Subsequently, a subgroup analysis (clinical trials vs. clinical practice) was carried out using the Cochran Q statistics (Deeks et al. 2003) as omnibus test, to explore whether the clinical and demographical characteristics of patients differ between the two groups. Results are presented in forest plots where the different characteristics examined are reported according to subgroup. Ninety-five percent CI were computed for individual studies (using the exact binomial method) and for the pooled estimate of clinical trials (according, as previously stated, to a random-effect model). All analyses were performed with R statistics (version 3.2.0), using the additional packages META e METAFOR. The significance level was set at $p < 0.05$.

Results

Demographic, clinical and biological characteristics of clinical practice patients

A total of 650 CP patients with HER2-positive EBC were enrolled in this study. Table 1 shows patients' clinical characteristics and adjuvant therapies in our dataset and in published clinical trials. In our dataset, median age was 55 years (range 27–93 years); 34 % (255) of patients were pre-menopausal and 65 % (396) were postmenopausal. Data on adjuvant chemotherapy was available for 553 patients. Most patients (97 %, 535) received adjuvant therapy, and the most frequently delivered chemotherapies were anthracyclines (12 %, 66 patients), taxanes (17 %, 93 patients) or combined treatment with anthracyclines followed by taxanes (68 %, 363 patients). Data on endocrine therapy were available for 548 patients, and most of them (70 %, 381 patients) received adjuvant hormone therapy. Data on trastuzumab adjuvant therapy were reported for 554 patients. Almost all CP patients (98 %, 542 patients) received adjuvant trastuzumab at least once.

The biological tumor characteristics in our dataset and published RCTs are reported in Table 2. In CP patients, 91 % (587) of EBCs were invasive ductal carcinomas, 3 % (22) were invasive lobular carcinomas, and 4 % (28) were other minor subtypes. Fifty-seven percent (369) of CP EBCs were poorly differentiated (G3). Overall, 59 % (387) of CP tumors were smaller than 2 cm, and 41 % (247) were larger than 2 cm. Moreover, 48 % (313) of CP tumors were free of lymph node metastases, 28 % (180) were associated with fewer than three metastatic nodes, and 15 % (101) had more than three metastatic nodes. Seventy-two percent (466) of CP EBCs were HR positive (ER positive and/or PgR positive); in detail, 70 % (458) were ER positive and 60 % (391) were PgR positive. All (650) CP EBCs were HER2 positive, as expected.

Comparison between CP patients and the RCT population

Compared to RCT women, CP patients were more likely to be older than 50 years (65 vs. 49 %; $Q = 64.31$, $p < 0.0001$; Fig. 1a) and to have a smaller tumor (tumor size ≥2 cm 39 vs. 59 %; $Q = 72.08$, $p < 0.0001$; Fig. 1b). They were less likely to have metastatic axillary nodes (metastatic nodes rate 47 vs. 89 %; $Q = 16.56$, $p < 0.0001$; Fig. 1c) and more likely to have a lower tumor grade (G3 rate 61 vs. 67 %; $Q = 5.09$, $p = 0.0241$; Fig. 1d). Overall, CP EBCs were more likely to be HR positive than the RCT counterpart (72 vs. 54 %; $Q = 67.62$, $p < 0.0001$; Fig. 2a). In detail, 71 % of CP tumors were ER positive versus 51 % of RCT tumors ($Q = 77.97$, $p < 0.0001$; Fig. 2b), whereas 60 % of CP tumors were PgR positive versus 39 % of RCT tumors ($Q = 92.75$, $p < 0.0001$; Fig. 2c). Neither tumor histotype nor menopausal status differed between the two groups.

Figure 3a–c shows the therapeutic strategies used in the two study groups. Clinical practice patients more frequently received adjuvant endocrine therapy (70 vs. 57 %, $Q = 13.17$, $p < 0.0003$; Fig. 3a) and slightly less frequently adjuvant chemotherapy (97 vs. 99.7 %; $Q = 22.16$,

Table 1 Population characteristics

Characteristics	BCIRG-006	FinHER	FNCLCC-PACS 04	HERA	NSABP B31	NCCTG N9831	CP population
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
	3222 (100)	1010 (100)−232 (100)[a]	528 (100)	3387 (100)	2101 (100)	1944 (100)	650 (100)
Age							
Median (years)	N/A	50.9	48	49	N/A	N/A	55
<50	1698 (53)	N/A	N/A	1741 (51)	1060 (50)	966 (50)	225 (34)
≥50	1524 (47)	N/A	N/A	1646 (49)	1041 (50)	978 (50)	421 (65)
Missing	0 (0)	N/A	N/A	0 (0)	0 (0)	0 (0)	4 (1)
Menopausal status							
Premenopausal	N/A	N/A	226 (43)	533 (16)	N/A	N/A	255 (39)
Postmenopausal	N/A	N/A	177 (33)	1576 (46)	N/A	N/A	395 (61)
Missing/uncertain	N/A	N/A	125 (24)	1278 (38)	N/A	N/A	0 (0)
CT adjuvant (CP N = 553)							
Yes	3222 (100)	232 (100)	528 (100)	3387 (100)	4006 (99)		535 (97)
No	0 (0)	0 (0)	0 (0)	0 (0)	39 (1)		18 (3)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)
CT Regimen (CP N = 535)							
Anthracyclines w/o taxanes	0 (0)	120 (52)	279 (53)	2307 (67)	0 (0)		66 (12)
Taxanes w/o anthracyclines	1075 (33)	0 (0)	0 (0)	206 (6)	0 (0)		93 (17)
Anthracyclines + taxanes	2147 (67)	112 (48)	249 (47)	873 (26)	4006 (100)		363 (68)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		9 (2)
Missing	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)		4 (1)
HT adjuvant (CP N = 548)							
Yes	1614 (50)	732 (73)	315 (60)	1710 (50)	1176 (56)	994 (51)	381 (70)
No	1608 (50)	278 (27)	213 (40)	1677 (50)	925 (44)	931 (48)	167 (30)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	19 (1)	0 (0)
Trastuzumab adjuvant, as planned (CP N = 554)							
Yes	2149 (67)	116 (50)	260 (49)	1694 (50)	2028 (50)		542 (98)
No	1073 (33)	116 (50)	268 (51)	1693 (50)	2017 (50)		12 (2)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)
Trastuzumab adjuvant, at least one time (CP N = 542)							
Yes	2126 (99)	115 (99)	234 (90)	1680 (99)	1845 (91)		542 (100)
No	23 (1)	1 (1)	26 (10)	20 (1)	183 (9)		0 (0)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)

CP clinical practice, *N/A* not available, *CT* chemotherapy, *HT* hormonal therapy, *w/o* without

[a] In the FinHER trial, the overall population enrolled accounted for 1010 patients, but only 232 of them are HER2 positive and are randomly assigned to either receive or not adjuvant trastuzumab. HT data are only reported for the overall population in the original paper

$p < 0.0001$; Fig. 3b) compared to RCT patients. Among chemo-treated patients, there was no difference in the type of drugs delivered. Surprisingly, our patients received at least one dose of trastuzumab slightly more frequently than RCT patients (100 vs. 96.49 %; $Q = 9.04$, $p = 0.024$; Fig. 3c).

Patients with hematologic and/or neurologic, hepatic, renal or cardiac disorders (such as myocardial infarction, severe uncontrolled arrhythmias and/or arrhythmias requiring regular therapy, poorly controlled hypertension, congestive heart failure and other significant illnesses) were not eligible for adjuvant RCT (Joensuu et al. 2006; Piccart-Gebhart et al. 2005; Romond et al. 2005; Slamon et al. 2011; Spielmann et al. 2009). On the contrary, as shown in Table 3, 43 % (271) of CP patients had comorbidities before starting adjuvant treatment:

Table 2 Tumor features

Features	BCIRG-006	FinHER	FNCLCC–PACS 04	HERA	NSABP B31	NCCTG N9831	CP population
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
	3222 (100)	232 (100)	528 (100)	3387 (100)	2101 (100)	1944 (100)	650 (100)
Histotype							
Ductal	N/A	209 (90)	495 (94)	N/A	N/A	N/A	587 (91)
Lobular	N/A	21 (9)	18 (3)	N/A	N/A	N/A	22 (3)
Other	N/A	2 (1)	14 (3)	N/A	N/A	N/A	28 (4)
Missing	N/A	0 (0)	1 (0)	N/A	N/A	N/A	13 (2)
Grade							
1–2	N/A	77 (33)	181 (34)	1187 (35)	652 (31)	539 (28)	238 (37)
3	N/A	150 (65)	343 (65)	2027 (60)	1407 (67)	1377 (71)	369 (57)
Missing	N/A	5 (2)	4 (1)	173 (5)	42 (2)	28 (1)	43 (6)
Ki67							
≤20 %	N/A	N/A	N/A	N/A	N/A	N/A	152 (23)
>20 %	N/A	N/A	N/A	N/A	N/A	N/A	467 (72)
Missing	N/A	N/A	N/A	N/A	N/A	N/A	31 (5)
T							
1	1283 (40)	81 (35)	235 (45)	1347 (40)	823 (39)	762 (39)	387 (59)
≥2	1936 (60)	150 (65)	285 (54)	1651 (49)	1246 (59)	1181 (61)	247 (38)
Missing	3 (0)	1 (0)	8 (1)	389 (11)	32 (2)	1 (0)	16 (3)
N							
0	922 (29)	37 (16)	0 (0)	1100 (32)	0 (0)	282 (14)	313 (48)
1–3	1238 (38)	122 (53)	307 (58)	972 (29)	1212 (58)	932 (48)	180 (28)
≥4	1062 (33)	73 (31)	221 (42)	953 (28)	889 (42)	729 (38)	101 (15)
Missing	0 (0)	0 (0)	0 (0)	362 (11)	0 (0)	1 (0)	56 (9)
ER							
Positive	N/A	109 (47)	N/A	N/A	1096 (52)	983 (51)	458 (70)
Negative	N/A	123 (53)	N/A	N/A	987 (47)	960 (49)	191 (29)
Missing	N/A	0 (0)	N/A	N/A	18 (1)	1 (0)	1 (1)
PgR							
Positive	N/A	79 (34)	N/A	N/A	832 (40)	752 (39)	391 (60)
Negative	N/A	153 (66)	N/A	N/A	1248 (59)	1188 (61)	257 (40)
Missing	N/A	0 (0)	N/A	N/A	21 (1)	4 (0)	2 (0)
HR							
Positive (ER+ and/or PgR+)	1733 (54)	109 (47)	315 (60)	1710 (51)	1176 (56)	994 (51)	466 (72)
Negative (ER− and PgR−)	1489 (46)	123 (53)	213 (40)	1615 (48)	907 (43)	950 (49)	182 (28)
Missing	0 (0)	0 (0)	0 (0)	62 (2)	18 (1)	0 (0)	2 (0)
HER2							
Positive	3222 (100)	232 (100)	526 (100)	3387 (100)	2101 (100)	1944 (100)	650 (100)
Negative	0 (0)	0 (0)	2 (0)	0 (0)	0 (0)	0 (0)	0 (0)

CP clinical practice, *T* tumor size, *N* nodal status, *ER* estrogen receptor, *PgR* progesterone receptor, *HR* hormone receptors

20 % of CP patients were affected by diverse cardiac disorders (7 % had arrhythmias, 5 % had congestive heart failure, 2 % had a history of myocardial infarction and 86 % had hypertension), 4 % had a neurologic disorder, and 4 % were affected by diabetes and 13 % by other illnesses.

Discussion

Our study provides evidence that most tumor and clinical characteristics differ significantly between CP and RCT patients. In particular, CP patients were older and had smaller, better differentiated and less advanced tumors

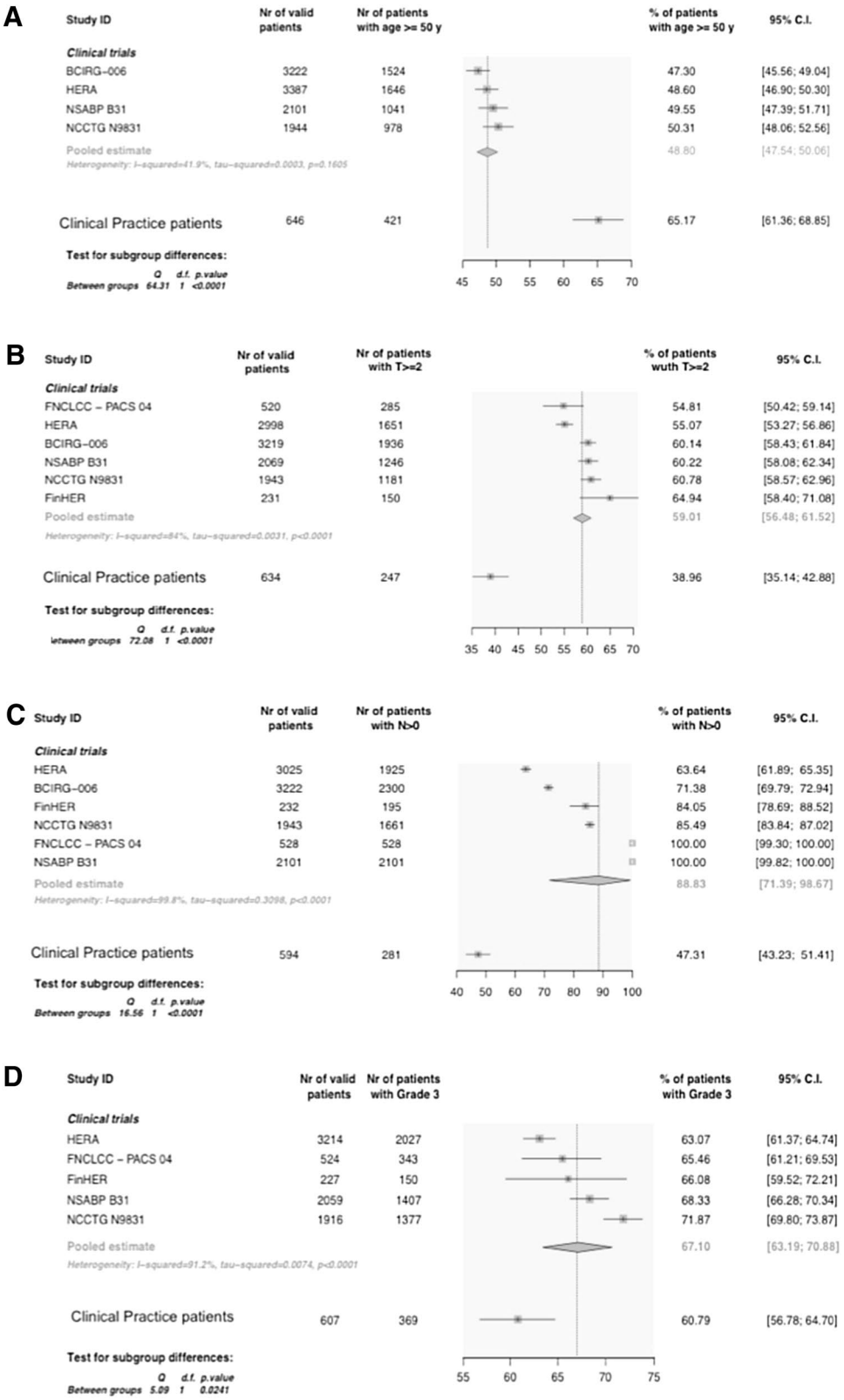

Fig. 1 Age, T, N and G comparison between CP and CT populations

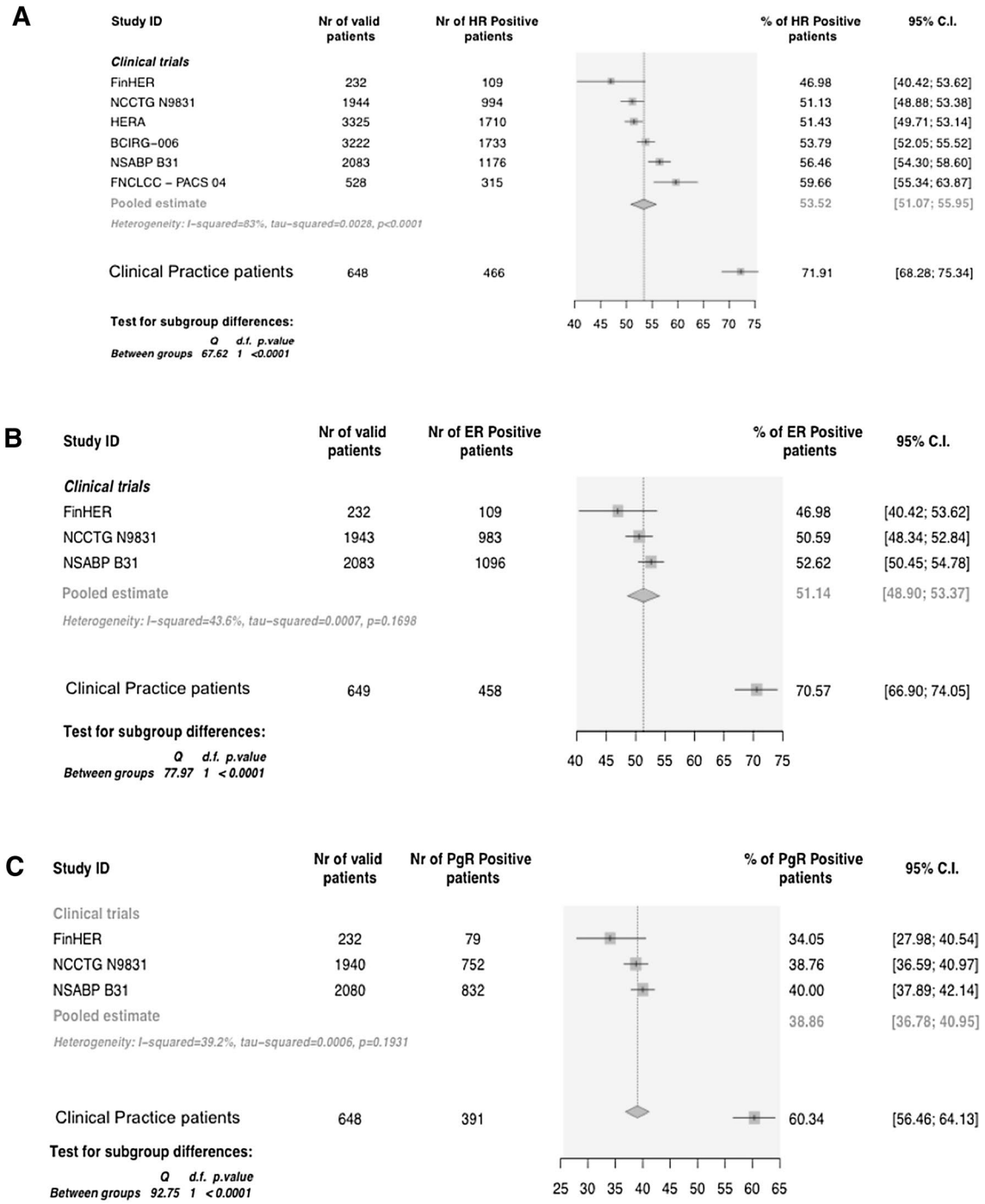

Fig. 2 Hormonal receptor status comparison between CP and CT populations

because they had fewer metastatic axillary nodes. Importantly, CP tumors were more endocrine sensitive than RCT tumors. Moreover, patients enrolled in RCTs had virtually no comorbidities because many of the latter were among the RCT exclusion criteria. On the contrary, most of our CP patients had health problems, mainly cardiac disorders, before cancer diagnosis. However, comorbidities, even cardiovascular disorders, did not preclude the use of trastuzumab in CP patients. Indeed, the rate of patients receiving at least one dose of trastuzumab was higher in CP patients than in RCT patients.

Undeniably, trastuzumab has changed the natural history of HER2-positive BC. Given the biological rationale of its mechanism of action and the extraordinary results

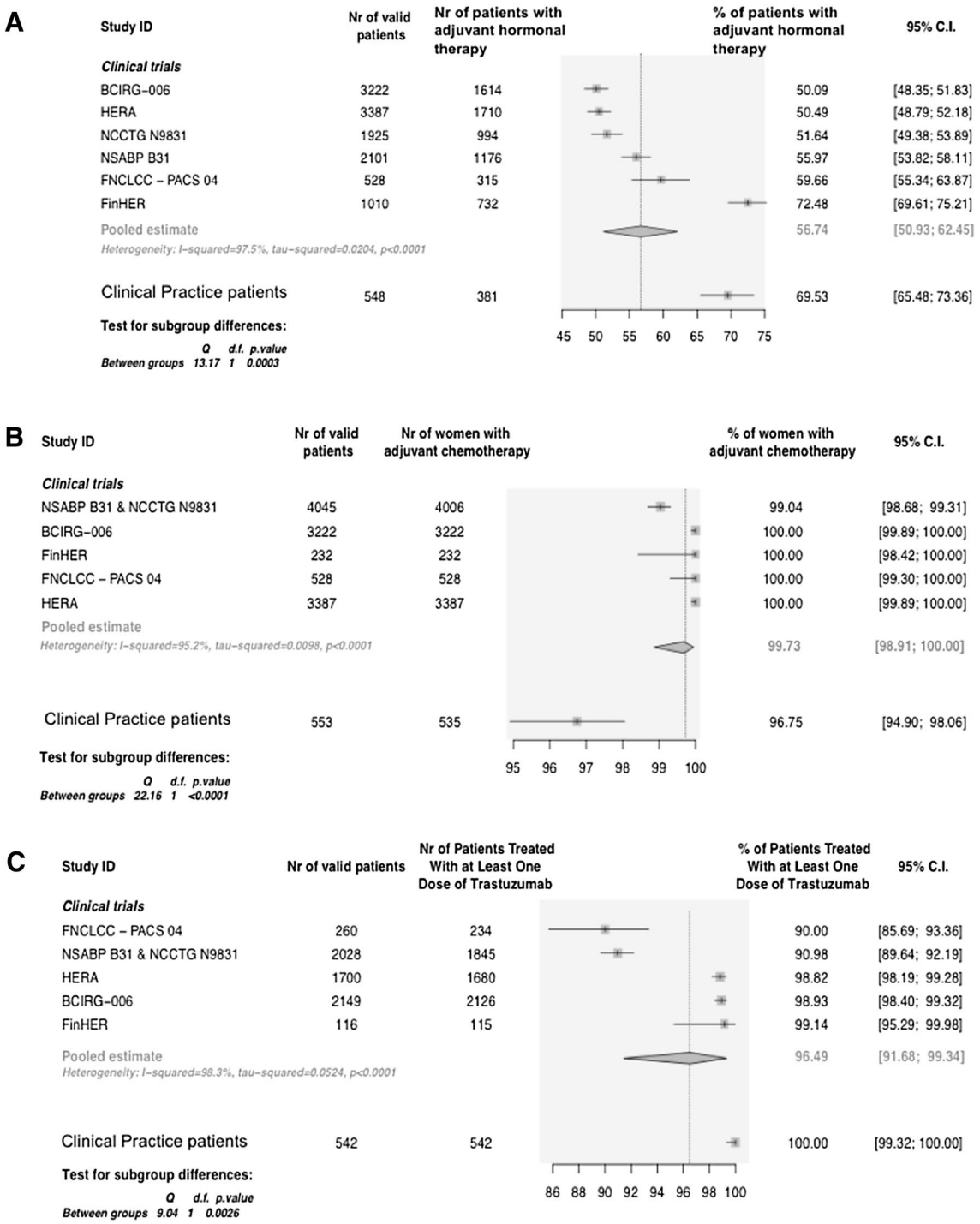

Fig. 3 Adjuvant therapeutic strategies compared between CP and CT populations

in both the preclinical (Baselga and Mendelsohn 1994; Baselga et al. 1998; Konecny et al. 2001; Pegram et al. 1998, 1999, 2000; Roche 2001) and clinical setting (Joensuu et al. 2006; Slamon et al. 2011; Spielmann et al. 2009; Piccart-Gebhart et al. 2005; Romond et al. 2005; Cobleigh et al. 1999; Slamon et al. 2001; Vogel et al. 2002; Seidman et al. 2008; Burstein et al. 2007; Robert et al. 2006; Von Minckwitz et al. 2008), the efficacy of trastuzumab is no longer questionable. However, we should not take it for granted that the safety and tolerability of this anticancer

Table 3 CP patients' comorbidities

Comorbidities	Yes *N* (%)	No *N* (%)	Missing *N* (%)	Overall *N* (%)
Neurologic disorders	25 (4)	360 (55)	265 (41)	650 (100)
Diabetes	28 (4)	475 (73)	147 (23)	650 (100)
Other	86 (13)	564 (87)	0 (0)	650 (100)
Cardiac Disorders	132 (20)	0 (0)	518 (80)	650 (100)

CP clinical practice

treatment in unselected CP patients are the same as that observed in RCT patients. Indeed, our study indicates that CP and RCT patients differ significantly in terms of tumor biology and clinical characteristics, most notably age and comorbidities. Because of these differences, the tolerability and safety profile of trastuzumab may also differ between the CP and RCT settings.

We did not include in our evaluation more recent RCTs exploring the use of combined anti-HER2 agents (Piccart-Gebhart et al. 2014; Pivot et al. 2013) because we focused on the use of trastuzumab as a single anti-HER2 agent in the adjuvant setting. We cannot exclude that the patients enrolled in these more recent studies are more similar to those we observed in the present analysis. Interestingly, our data also suggest that trastuzumab is much more frequently administered in CP than would be expected from a simple extrapolation of RCT data, because in "real life", oncologists are prone to start trastuzumab even when patients have comorbidities.

Conclusions

In conclusion, our data suggest that the efficacy and tolerability of therapies should be assessed also in a clinical scenario closer to routine CP to further validate RCT results and to understand how well an anticancer agent works in a less restricted setting when it's more widely used.

Acknowledgments We gratefully thank CR technology S.r.l. in the person of Luciano Di Pierno, for designing the online database and extracting all patient's data for statistical analysis. We also thank Ms. Jane Gilder for her punctual revision and correction of the paper draft.

Author's contributions G.A., M.E.C., S.D.P., L.B., A.M. and C.Z. conceived of the study and participated in its design. All authors contributed in enrolling patients and collecting data. D.B. performed the statistical analysis. G.A., M.G. and F.S. wrote the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors themselves financed this study and declared no conflict of interests.

References

Baselga J, Mendelsohn J (1994) Receptor blockade with monoclonal antibodies as anti-cancer therapy. Pharmacol Ther 64:127–154

Baselga J, Norton L, Albanell J et al. (1998) Recombinant humanized anti-HER2 antibody (Herceptin) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/neu-overexpressing human breast cancer xenografts. Cancer Research 58:2825–2831

Baselga J, Cortez H, Kim SB et al (2012) Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 366:109–119

Burstein HJ, Keshaviah A, Baron AD et al (2007) Trastuzumab plus vinorelbine or taxane chemotherapy for HER2-overexpressing metastatic breast cancer: the trastuzumab and vinorelbine or taxane study. Cancer 110:965–972

Chia S, Norris B, Speers C et al (2009) Human epidermal growth factor receptor 2 overexpression as a prognostic factor in a large tissue microarray series of node-negative breast cancers. J Clin Oncol 26:5697–5704

Cobleigh MA, Vogel CL, Tripathy D et al (1999) Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 17:2639–2648

Coussens L, Yang-Feng TL, Liao YC et al (1985) Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. Science 230:1132–1139

Curigliano G, Viale G, Bagnardi V et al (2009) Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. J Clin Oncol 27:5693–5699

Deeks J, Higgins J, Altman D (2003) Cochrane reviewers' handbook 4.2.1. Wiley, Chichester

DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188

Freeman MF, Tukey JW (1950) Transformations related to the angular and the square root. Ann Math Stat 21:607–611

Gonzalez-Angulo AM, Litton JK, Broglio KR et al (2009) High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. J Clin Oncol 27:5700–5706

Joensuu H, Kellokumpu-Lehtinen PL, Bono P et al (2006) Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 354:809–820

Konecny G, Fritz M, Untch M, et al. (2001) HER-2/neu overexpression and in vitro chemosensitivity to CMF and FEC in primary breast cancer. Breast Cancer Res Treat 69:53–63

Miller JJ (1978) The inverse of the Freeman-Tuckey double arcsine transformation. Am Stat 32:138

Pegram MD, Lipton A, Hayes DF et al. (1998) Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/neu monoclonal antibody plus cisplatin in patients with HER2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment. Journal of Clinical Oncology 16:2659–2671

Pegram M, Hsu S, Lewis G et al. (1999) Inhibitory effects of combinations of HER-2/neu antibody and chemotherapeutic agents used for treatment of human breast cancers. Oncogene 18:2241–2251

Pegram MD, Lopez A, Konecny G et al. (2000) Trastuzumab and chemotherapeutics: drug interactions and synergies. Seminars in Oncology 27(6 Suppl 11):21–25 (discussion 92–100)

Perou CM, Sørlie T, Eisen MB et al (2000) Molecular portraits of human breast tumours. Nature 406:747–752

Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353:1659–1672

Piccart-Gebhart MJ, Holmes AP, Baselga J et al (2014) First results from the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L), or their combination (T + L) in the adjuvant treatment of HER2-positive early breast cancer (EBC). J Clin Oncol 32:5s (suppl; abstr LBA4)

Pivot X, Romieu G, Debled M et al (2013) 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. Lancet Oncol 14(8):741–748

Robert N, Leyland-Jones B, Asmar L et al (2006) Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. J Clin Oncol 24:2786–2792

Roche (2001) Herceptin product monograph. Gardiner-Caldwell Communications Ltd, Macclesfield

Romond EH, Perez EA, Bryant J et al (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353:1673–1684

Seidman A, Berry DA, Cirrincione C et al (2008) Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 non overexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol 26:1642–1649

Slamon DJ, Clark GM, Wong SG et al (1987a) Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235:177–182

Slamon D, Clark GM, Wong S et al (1987b) Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235:177–182

Slamon DJ, Godolphin W, Jones LA et al (1989) Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 244:707–712

Slamon DJ, Leyland-Jones B, Shak S et al (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783–792

Slamon D, Eiermann W, Roberto N et al (2011) Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365:1273–1283

Spielmann M, Rochè H, Delozier T et al (2009) Trastuzumab for patients with axillary-node–positive breast cancer: results of the FNCLCC-PACS 04 trial. J Clin Oncol 27:6129–6134

Verma S, Miles D, Gianni L et al (2012) Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 367:1783–1791

Vogel CL, Cobleigh MA, Tripathy D et al (2002) Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 20:719–726

Von Minckwitz G, Zielinski C, Maarteense E et al (2008) Capecitabine vs. capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: The TBP phase III study (GBG 26/BIG 3-05) [abstract]. J Clin Oncol 26(Suppl 15):Abstract 1025

Wolff AC, Hammond ME, Schwartz JN et al (2007a) American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 25:118–145

Wolff AC, Hammond MEH, Schwartz JN et al (2007b) Guideline for HER2 testing in breast cancer. Arch Pathol Lab Med 131:18–43