Available online at www.sciencedirect.com
ScienceDirect
EJSO xx (2011) 1–8
EJSO the Journal of Cancer Surgery
www.ejso.com

Surgery following neoadjuvant therapy in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herceptin (NOAH) study ☆

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Accepted 25 July 2011

Abstract

Aim: To describe surgical outcomes in patients with HER2-positive locally advanced (LABC) or inflammatory breast cancer (IBC) participating in the NeOAdjuvant Herceptin (NOAH) study (ISRCTN86043495).
Patients and methods: A total of 235 patients with HER2-positive disease were randomized to neoadjuvant trastuzumab plus chemotherapy (doxorubicin plus paclitaxel, followed by paclitaxel, followed by cyclophosphamide, methotrexate and fluorouracil) or neoadjuvant chemotherapy alone. Of these patients, 228 received their allocated treatment (115 received trastuzumab plus chemotherapy and 113 received chemotherapy alone) and were potentially eligible for surgery. Mastectomy was required for all patients with IBC and was recommended for all patients with LABC. However, breast-conserving therapy could be considered for patients with peripheral neoplasms measuring $\leq$4 cm in diameter at diagnosis, with a favorable ratio of tumor to breast volume, or at the patient's request if there had been a good response to treatment.
Results: As previously reported, the addition of trastuzumab to neoadjuvant chemotherapy improved the overall, complete and pathological complete response to therapy and significantly improved event-free survival (the primary endpoint of the study). Trastuzumab also enabled more patients to have breast conserving surgery (BCS) (23% versus 13% respectively) without an apparent detrimental effect on local disease control (no patient treated with trastuzumab plus chemotherapy had experienced a local recurrence after BCS at the time of analysis).
Conclusions: Although this was not an aim of the trial, neoadjuvant trastuzumab given concurrently with chemotherapy enabled 23% of patients with HER2-positive LABC/IBC to avoid mastectomy (including a small number of patients with IBC).

Keywords: Neoadjuvant chemotherapy; Locally advanced breast cancer; Conservative surgery; Trastuzumab; Pathological complete remission; pCR

Introduction

Up to 10% of patients with breast cancer present with locally advanced (LABC) or inflammatory breast cancer (IBC) in the Western world, where the incidence of LABC appears to be declining while the incidence of IBC rises.[1,2] Despite recent improvements in survival, the outlook for patients with LABC (median survival 6.4 years) is worse than for patients with early (operable) breast cancer (EBC) (median

☆ *Statement of Originality*: The main safety and efficacy data from the trial have previously been presented at international conferences (Gianni et al., ASCO 2007; Baselga et al., ECCO 2007; Eiermann et al., EBCC 2008; Gianni et al., SABCs 2008) and published (Gianni et al., Lancet 375; 377–384, 2010). Preliminary data on surgical aspects of the trial have been presented at an international conference (Semiglazov et al., EBCC 2008).

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doi:10.1016/j.ejso.2011.07.003

Please cite this article in press as: Semiglazov V, et al., Surgery following neoadjuvant therapy in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herceptin (NOAH) study, Eur J Surg Oncol (2011), doi:10.1016/j.ejso.2011.07.003

survival >10 years) but better than for patients with IBC (median survival 2.9 years).[1] Pre-operative, systemic (neoadjuvant) therapy, preferably including an anthracycline and a taxane, is the treatment of choice for patients with LABC and IBC since in both conditions the disease is inoperable at diagnosis (stage IIIA or IIIB for non-inflammatory LABC and stage IIIB for IBC).[3,4] Pre-operative therapy improves operability, sometimes allowing breast conserving surgery (BCS) to take place in patients with non-inflammatory LABC, as well as treating occult micro-metastases.[5] For patients with IBC, mastectomy is recommended rather than BCS following neoadjuvant therapy, because of the diffuse pattern of breast infiltration which characterizes the disease, the high risk of local recurrence (as well as distant metastases), and the poor prognosis associated with disease relapse. In most series, trimodality therapy (chemotherapy, radiotherapy and mastectomy) has been found to improve local disease control[6–9] and even survival,[10,11] compared to bimodality therapy (chemotherapy and radiotherapy only).

Trastuzumab (Herceptin®, Roche), a humanized monoclonal antibody which targets the human epidermal growth factor receptor-2 (HER2), is approved for use in patients with metastatic[12,13] and early, operable breast cancer[14–16] whose tumors show amplification and/or strong overexpression of HER2. It has been shown to have efficacy alone[17,18] and in combination with a range of cytotoxic agents[12,13,15,16,19,20] and hormone therapy[21] in patients with HER2-positive disease. IBC is more frequently HER2-positive than other forms of breast cancer and HER2-positive IBC has been found to be responsive to trastuzumab and other HER2-targeted agents.[22–26]

The NeOAdjuvant Herceptin (NOAH) study (Roche study number MO16432, ISRCTN86043495) was designed to evaluate the addition of trastuzumab to neoadjuvant chemotherapy in patients with HER2-positive LABC/IBC. The trial also included a parallel cohort of patients with HER2-negative LABC/IBC, who received chemotherapy alone. A sequential chemotherapy regimen was selected for all patients, and this included a taxane (paclitaxel), an anthracycline (doxorubicin) and cyclophosphamide, methotrexate and fluorouracil (CMF). The main safety and efficacy results of this trial have already been reported.[27] Surgical outcomes in the HER2-positive groups of patients are presented here.

Patients and methods

Study design

This was a multicenter, international, open-label, randomized phase III study conducted in 27 centers in six countries. Treatment was allocated centrally using a minimization algorithm with stratification for disease stage, hormone receptor status, and study site location. Patients with HER2-positive disease (defined as 3 + overexpression by immunohistochemistry or HER2 amplification by fluorescent in-situ hybridization, according to a central laboratory) were randomly assigned to chemotherapy alone or chemotherapy plus neoadjuvant (and adjuvant) trastuzumab. The study was approved by local ethics committees. Written informed consent was obtained from all patients.

Patients

To enter the study, patients had to be female, at least 18 years old, with previously untreated, histologically-proven, unilateral LABC, defined as T3N1 or T4 (skin or nipple invasion, peau d'orange, extension into chest wall or inflammatory carcinoma), or any T plus N2 or N3, or any T plus involvement of ipsilateral supraclavicular nodes. Patients also had to have at least one measurable lesion (unless they had IBC). Other requirements included a good performance status, no concurrent serious medical conditions, adequate bone marrow, renal and liver function, and a left ventricular ejection fraction (LVEF) $\geq$ 55%.

Systemic treatment

All patients received the following intravenous neoadjuvant chemotherapy regimen: doxorubicin 60 mg/m^2 plus paclitaxel 150 mg/m^2 infused over 3 h, every 3 weeks for three cycles, followed by paclitaxel 175 mg/m^2 administered every 3 weeks for four cycles, followed by cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2 and fluorouracil 600 mg/m^2 on days 1 and 8 every 4 weeks for three cycles. Patients allocated to trastuzumab received a loading dose of 8 mg/kg infused intravenously over 90 min, followed by 10 cycles of 6 mg/kg given over 30 min every 3 weeks during chemotherapy (every 4 weeks during CMF, if preferred). Trastuzumab continued after surgery for a total of one year of trastuzumab treatment. Adjuvant hormone therapy, if indicated, was started after surgery. No adjuvant postoperative chemotherapy was given.

Surgery

Surgery was scheduled between 14 and 28 days after the last cycle of chemotherapy, assuming resolution of any hematological or infective complications. Radical mastectomy was mandatory (regardless of clinical/radiological findings after chemotherapy) for all patients with IBC, or with tumors measuring >5 cm at diagnosis, or with microcalcifications involving more than one quadrant of the breast. Breast conserving surgery (BCS) could be considered for patients with peripheral neoplasms (mammary fold or axillary tail) measuring $\leq$4 cm in maximum diameter at diagnosis, if a good cosmetic result was anticipated (based on the ratio of tumor diameter to breast volume). Breast conserving surgery could also be considered upon patient request, if the patient had achieved an objective response to treatment (>50% reduction in tumor size) with

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no residual edema or peau d'orange, and a good cosmetic result was expected. It was recommended that breast reconstruction with implants after mastectomy be discussed and agreed with the radiotherapist first.

Axillary lymph node dissection was preferred up to the third level but dissection of the first two levels was acceptable. Nodal sampling or first level dissection was not considered adequate.

Radiotherapy

In all patients, starting within 4 weeks of surgery, postoperative radiotherapy was to be delivered according to protocol indications derived from the guidelines of the American Society of Clinical Oncology (ASCO) and the American Society for Therapeutic Radiology and Oncology (ASTRO). Briefly, patients subjected to radical mastectomy should receive chest wall irradiation, while patients subjected to conservative surgery should receive whole breast irradiation and tumor breast boost was recommended. Axillary and supraclavicular irradiation was dependent on the pathological status of these two areas. The effect of concurrent radiotherapy and trastuzumab had not been studied at the time the NOAH study started and there were concerns about possibly increased cardiotoxicity if the radiation fields included the heart. Accordingly, investigators were advised not to irradiate the internal mammary nodes and were allowed to delay the start of adjuvant trastuzumab until after completion of radiotherapy if they wished.

Efficacy assessments

Patients were assessed for tumor response by physical examination prior to every new phase of chemotherapy, and by mammogram or ultrasound at baseline and before surgery. Subsequently, patients were checked for possible disease recurrence at regular intervals until 10 years after surgery, as previously described.[27] Cytological or histological confirmation was required for local or regional recurrence or contralateral invasive breast cancer. All surgical specimens were evaluated for residual invasive or in-situ disease.

Safety assessments

Adverse events were assessed clinically and by laboratory methods throughout chemotherapy, and were graded according to National Cancer Institute common toxicity criteria version 2.0, as described previously.[27] Cardiac function was monitored clinically and by electrocardiogram and LVEF measurements throughout treatment.

Statistical analyses

The primary objective of the NOAH study was event-free survival (EFS). The study was powered to detect an absolute improvement of 18.5% (corresponding to a 68.5% EFS rate at 3 years) in patients with HER2-positive disease treated with trastuzumab, assuming a 3 year EFS rate of 50% in patients with HER2-positive disease treated with chemotherapy alone, as previously described.[27] On the basis of these assumptions, enrollment of 116 patients was planned for each of the two HER2-positive arms of the study. Secondary objectives included comparison of clinical and pathological response rates, survival, and safety between the three groups of patients. Exploratory analyses of surgical outcomes were planned although they were not a study endpoint. The main efficacy analyses for the study overall were conducted on an intent-to-treat basis, as previously described,[27] but for the exploratory comparisons of surgical outcome described here, patients were analyzed according to treatment actually received (per protocol). Patients who did not start their allocated neoadjuvant therapy regimen or who were not subjected to surgery were not included in the comparisons of surgical outcome. Frequencies of BCS were compared by use of chi-square test. The cumulative risk of local recurrences was measured from the date of surgery to the date of the event and data are based on the same data cut-off as for the main study results. At this time (median follow-up 3.2 years), all patients had completed neoadjuvant therapy and surgery.

Results

Patients

A total of 235 patients with newly diagnosed HER2-positive LABC/IBC entered the study between June 20, 2002 and December 12, 2005 and were randomized to trastuzumab plus chemotherapy ($n = 117$) or chemotherapy alone (118). Two hundred and twenty eight patients received their allocated treatment (115 patients randomized to trastuzumab plus chemotherapy and 113 patients allocated to chemotherapy alone). Baseline characteristics for the 228 treated patients with HER2-positive disease are summarized in Table 1. There were no major differences between the two arms.

Overall response to neoadjuvant therapy

As previously reported,[27] the great majority of patients with HER2-positive disease responded to neoadjuvant therapy (Table 2). Compared to patients treated with chemotherapy alone, more patients treated with trastuzumab plus chemotherapy had an objective clinical response to therapy (89% of patients treated with chemotherapy plus trastuzumab versus 77% of patients treated with chemotherapy alone), and more patients achieved a pathological complete response in the breast alone (pCR) (43% versus 23%, respectively) and in the breast and axillary lymph nodes (tpCR) (39% versus 20%, respectively).

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Table 1
Pretreatment characteristics of patients with HER2-positive disease treated with neoadjuvant chemotherapy, with or without trastuzumab.

	Trastuzumab + chemotherapy	Chemotherapy alone
Total treated	115 (100%)	113 (100%)
Disease stage		
Non inflammatory disease	84 (73%)	82 (73%)
Inflammatory disease	31 (27%)	31 (27%)
Clinical nodal status		
N0	15 (13%)	18 (16%)
N1	47 (41%)	49 (43%)
N2	46 (40%)	41 (36%)
N3	7 (6%)	5 (4%)
Hormonal receptors		
ER and/or PgR positive	40 (35%)	40 (35%)
Both negative	75 (65%)	73 (65%)

Surgery

The great majority of patients underwent surgery as planned (Table 3). The main reason for not having surgery (in both treatment arms) was because the disease was still considered inoperable after completion of neoadjuvant therapy. However, most patients in this category had actually responded to treatment and even achieved a complete clinical response (CR) according to the investigator but had residual edema. More patients treated with trastuzumab plus chemotherapy were able to undergo surgery (83% versus 78% of patients treated with chemotherapy alone), and more patients treated with trastuzumab plus chemotherapy were able to have BCS (23%, 95% Cl 15–33) versus 13% (95% Cl 6–21) of patients treated with chemotherapy alone). The difference in rate of BCS between the two arms was not statistically significant ($p = 0.07$) and, anyway, such an exploratory statistical comparison needs to be interpreted with care since it was not part of the preplanned efficacy analyses and was not adjusted for multiplicity of testing.

Table 3
Type of surgery undertaken in patients with HER2-positive disease treated with neoadjuvant chemotherapy, with or without trastuzumab.

	Trastuzumab + chemotherapy	Chemotherapy alone
Total treated	115 (100%)	113 (100%)
Subjected to surgery	96 (83%)	88 (78%)
- Conservative surgery	22 (23%, 95% CI15–33)*	11 (13%, 95% CI6–21)*
- Mastectomy	74 (77%, 95% CI 67–85)*	77 (88%, 95% CI 79–94)*
Not subjected to surgery	19 (17%)	25 (22%)
- PD during therapy	4 (3%)	7 (6%)
- Judged inoperable by PI[a]	10 (7%)	12 (11%)
- Refused surgery	3[b]	2[c]
- Consent withdrawal	2	4

95% CI: 95% confidence interval.
* $P = 0.07$.
[a] All patients were considered inoperable by the investigator due to residual edema. However, all achieved a clinical CR or PR.
[b] 2 of these patients had achieved a clinical CR.
[c] 1 of these patients had achieved a clinical CR.

Exploratory analysis of baseline factors suggests that all subgroups of patients were more likely to undergo BCS after trastuzumab plus chemotherapy compared with chemotherapy alone (Table 4). The difference was most marked for patients with non-inflammatory breast cancer (26% vs 14%) and patients with hormone receptor negative disease (21% vs 5%), suggesting that these patients might be particularly responsive to neoadjuvant trastuzumab in combination with chemotherapy. However, very few patients with IBC underwent BCS (6 patients in total: 4 treated with trastuzumab plus chemotherapy and 2 treated with chemotherapy alone) because the protocol specifically recommended mastectomy for patients with IBC (regardless of

Table 2
Clinical and pathological response in patients with HER2-positive disease treated with neoadjuvant chemotherapy, with or without trastuzumab.

	Trastuzumab + chemotherapy		Chemotherapy alone		*P*-value
	N (%)	95% CI	*N* (%)	95% CI	
Total patients treated	115 (100%)		113 (100%)		
Objective clinical remission (CR + PR) rate	102 (89%)	81–94%	87 (77%)	68–84%	0.019
pCR	50 (43%)	34–53%	26 (23%)	16–32%	0.001
ptCR	45 (39%)	30–49%	23 (20%)	13–29%	0.002
Patients who underwent surgery	96 (100%)		88 (100%)		
Objective clinical response (CR + PR) rate	89 (93%)	86–97%	74 (84%)	75–91%	0.07
pCR	50 (52%)	42–62%	26 (30%)	20–40%	0.002
ptCR	45 (47%)	37–57%	23 (26%)	17–37%	0.004

pCR: complete pathological remission in breast only.
ptCR: complete pathological remission in breast and homolateral axillary nodes.

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Table 4
Frequency of conservative surgery according to main pre-treatment and post-treatment characteristics.

	Trastuzumab + chemotherapy % BCS (95% CI)	Chemotherapy alone % BCS (95% CI)
Disease stage		
Non inflammatory	26 (16–38) *	14 (7–25) *
Inflammatory	15 (4–35)	9 (1–28)
Hormonal receptors		
ER and/or PgR positive	27 (13–46)	24 (11–42)
Both negative	21 (11–33) **	5 (1–15) **
Largest tumor dimension		
<=2.0 cm	50 (12–88)	0
2.1–5.0 cm	29 (15–46)	18 (7–35)
>5.0 cm or non measurable	16 (8–29)	10 (3–21)
Clinical remission status		
CR + PR	25 (16–35) ***	11 (5–20) ***
No response	0	21 (5–51)

95% CI: 95% confidence interval.
* $P = 0.085$; ** $P = 0.016$; *** $P = 0.022$.

response to neoadjuvant therapy). Thus it is not possible to draw any conclusions regarding differences in rates of BCS with trastuzumab plus chemotherapy in patients with inflammatory versus non-inflammatory disease.

Exploratory analysis of post-treatment characteristics also showed that all subgroups of patients were more likely to undergo BCS after trastuzumab plus chemotherapy compared with chemotherapy alone (Table 4). Thus, for example, 25% of patients who achieved a clinical CR or partial response (PR) to therapy underwent BCS after trastuzumab plus chemotherapy, compared to only 11% of patients after chemotherapy alone ($P = 0.022$). This finding suggests that perhaps the quality of CR and/or PR was 'better' in the trastuzumab plus chemotherapy arm compared with the chemotherapy alone arm, making it more likely that the surgeon would consider the patient suitable for conservative surgery. This view is supported to some extent by a comparison of pathological and clinical findings (Table 5). Comparing pathological CR rates with pre-operative clinical response status reveals a close correlation between clinical and pathological findings, so that in both treatment arms, patients who achieved a clinical CR were more likely to have achieved a pathological CR than patients who only achieved a clinical PR. However, overall, patients treated with trastuzumab plus chemotherapy were more likely to have achieved a pathological CR than patients treated with chemotherapy alone, and this applied to patients who achieved a clinical CR and to patients who achieved a clinical PR.

Table 5
Relationship between clinical response and pathological complete response in breast in patients who underwent surgery.

Pathological/clinical response	Trastuzumab + chemotherapy		Chemotherapy alone	
	N	%	N	%
pCR/cCR	42/63	67	23/47	49
pCR/cPR	5/26	19	2/27	7
pCR/cNR	0/1	0	0/6	0
pCR/cNA	3/6	50	1/8	13

pCR: complete pathological response in breast only.
cCR: clinical complete pathological response.
cPR: clinical partial response.
cNR: clinical no response (ie. stable disease).
cNA: clinically not assessable.

Local recurrence rates

Overall, one year of adjuvant trastuzumab started concurrently with neoadjuvant chemotherapy significantly improved EFS in patients with HER2-positive LABC/IBC, as described previously.[27] Local, regional and distant recurrences were all less frequent in patients treated with trastuzumab plus chemotherapy when analyzed on an intent-to-treat basis. Since the type of surgery may influence local recurrence rates, the cumulative risk of local recurrence (defined as a histologically or cytologically-confirmed recurrence in the ipsilateral breast after conservative surgery or in the soft tissue or skin of the ipsilateral chest wall after mastectomy) as the first or only site of recurrence was evaluated in patients who had a mastectomy or BCS (Table 6). Overall, at the time of reporting, only 6 patients had experienced such a recurrence, although follow-up time was relatively short (median 3.2 years). The rate was similar in patients who had had a mastectomy or BCS and in patients treated with trastuzumab plus chemotherapy or chemotherapy alone. However, no patients treated with trastuzumab plus chemotherapy had experienced a local recurrence after BCS (including the 4 patients with IBC in this group) suggesting that conservative surgery did not have a major detrimental effect on local disease control in these patients.

Safety

The safety of neoadjuvant trastuzumab in combination with sequential anthracycline and taxane-based neoadjuvant chemotherapy is described elsewhere.[27] In brief, the addition of trastuzumab was well tolerated with no major increase in grade 3 or 4 non-cardiac toxicity and no

Table 6
Cumulative risk of local recurrence as first and only type of recurrence.

	Chemotherapy plus trastuzumab		Chemotherapy alone	
	N events/ N patients	% Risk (95% CI)	N events/ N patients	% Risk (95% CI)
Conservative surgery	0/22	–	2/11	21 (0–48)
Mastectomy	2/74	3 (0–8)	2/77	3 (0–6)

95% CI: 95% confidence interval.

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unexpected serious adverse events. Most declines in LVEF were only grade 1 in severity. Two patients experienced a grade 2 (asymptomatic) decrease in LVEF and two patients developed congestive heart failure (New York Heart Association class III), which was reversible in both cases.

Discussion

Context for surgical results

The main results of the NOAH study have already been published.[27] These showed a significant improvement in the primary endpoint, EFS, in patients with HER2-positive LABC/IBC, when one year of neoadjuvant (and adjuvant) trastuzumab was incorporated into a sequential neoadjuvant regimen of non-cross-resistant, anthracycline- and taxane-based chemotherapy (3-year EFS 71% with trastuzumab plus chemotherapy versus 56% with chemotherapy alone; hazard ratio 0.59, 95% CI 0.38–0.90; $p = 0.013$). Overall response rate and clinical and pathological CR rates in breast and axillary lymph nodes, were also significantly increased. Improvement in operability and in the rate of BCS were not efficacy endpoints for the study since other endpoints (notably pathological CR rate) are more predictive of long term outcome.[8,28–30] Although higher rates of operability are clearly desirable, it is important that any increase in BCS does not result in inferior local disease control. This is especially important for patients with IBC, for whom mastectomy is currently considered standard surgical treatment.[3,4] Local relapse in patients with IBC is almost always followed by distant metastases and death.[11,31]

Higher rate of BCS with trastuzumab-based neoadjuvant therapy

Consistent with the higher rate of overall and clinical CR in patients treated with trastuzumab plus chemotherapy, more patients were able to undergo surgery following completion of neoadjuvant treatment (83% versus 78% of patients treated with chemotherapy alone). In addition, almost twice as many patients treated with trastuzumab plus chemotherapy were able to have BCS (23% versus 13% of patients treated with chemotherapy alone). Since BCS was only allowed for carefully selected patients with non-inflammatory disease, a the difference in rates of BCS was expected to be small in this study. Although not recommended by the protocol, patients treated with BCS included some women with IBC (four treated with trastuzumab plus chemotherapy, and two treated with chemotherapy alone). Fortunately, rates of local recurrence alone or as a first site of relapse, were low in the study overall with no noticeable difference between patients undergoing mastectomy or BCS. At the time of present analysis, none of the patients treated with trastuzumab plus chemotherapy followed by BCS have relapsed locally (including the four patients with IBC). These findings suggest that local disease control was generally good with the multimodality treatment used in this study and that control of systemic disease remains the main problem for patients with HER2-positive LABC/IBC.

Possible confounding factors

Although the higher rate of BCS observed in the trastuzumab-treated patients was probably a refection of the higher overall and clinical CR rates in this arm of the study, there are other possible reasons. Although baseline demographic and disease characteristics were well balanced between the two treatment arms, details of factors influencing choice of surgery were not collected. In particular, patient or surgeon preference were not available for the two treatment arms. An imbalance in these factors could account for the higher rate of BCS in patients treated with trastuzumab plus chemotherapy. Since the study was not blinded, patient or clinician bias could also have influenced the rate of BCS. For example, a belief in the superiority of trastuzumab plus chemotherapy could have led to a greater willingness to perform or request BCS in the trastuzumab arm of the study. Such bias could also have affected surgeons' assessments of overall operability.

Conclusion

Present data suggest that in addition to improving long-term outcomes, combining trastuzumab with neoadjuvant chemotherapy improved operability and allowed selected patients with LABC to avoid mastectomy. The data suggest that trastuzumab-based neoadjuvant therapy might possibly allow selected patients with IBC to have BCS in the future, although such an approach cannot currently be recommended and should be evaluated first in a randomized controlled trial.

Potential conflict of interest

Dr. Luca Gianni, co-author of the above manuscript, is member of the Advisory Board of the following entities: ROCHE, GENENTECH, GSK, WYETH, NOVARTIS, EISAI, PFIZER, MILLENNIUM TAKEDA, SANOFI AVENTIS, BOEHRINGER INGELHEIM, BIOGEN IDEC, ASTRA ZENECA.

Acknowledgments

We would like to thank all the patients who participated in our clinical trial and the many associates who made the trial possible. In particular, we thank the surgeons, radiotherapists, pathologists, medical oncologists, research nurses and data managers, including Alberto Berti, Lidia Mariani, and Claudia Tomezzoli from the Michelangelo operations office and Viviana Bentata from SOLTI, for study

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coordination and data management. We would also like to thank Dr Claire Barton for assistance in preparing the manuscript.

Research Support: F. Hoffmann-La Roche provided trastuzumab and financial support for the trial but was not involved in data collection or analysis. The Michelangelo group was responsible for data gathering and analysis. The corresponding author had responsibility for the decision to submit this manuscript for publication.

Appendix 1. List of active NOAH participating centers

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Russian Cancer Research Center, Moscow, Russia: S Tjulandin, M Lichinitser.

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Hospital de San Pau, Barcelona, Spain: B Ojeda.

Hospital Clinico Universitario, Zaragoza, Spain: J I Mayordomo.

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National Surgical Adjuvant Breast and Bowel Project, Pittsburgh, PA, USA: J Bryant (international advisory board member).

M D Anderson Cancer Center, Houston, TX, USA: G N Hortobagyi (international advisory board member).

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Please cite this article in press as: Semiglazov V, et al., Surgery following neoadjuvant therapy in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herceptin (NOAH) study, Eur J Surg Oncol (2011), doi:10.1016/j.ejso.2011.07.003