Ten-year survival of neoadjuvant dual HER2 blockade in patients with HER2-positive breast cancer

Nuciforo, P.; Townend, J.; Piccart, M.J.; Fielding, S.; Gkolfi, P.; El-Abed, S.; ... ; Cosimo, S. di

European Journal of Cancer 181 (2023) 92–101

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Ten-year survival of neoadjuvant dual HER2 blockade in patients with HER2-positive breast cancer

Paolo Nuciforo [a,*], John Townend [b], Martine J. Piccart [c], Shona Fielding [b], Panagiota Gkolfi [d], Sarra El-Abed [e], Evandro de Azambuja [c], Gustavo Werutsky [f], Judith Bliss [g], Volker Moebus [h], Marco Colleoni [i], Alvaro Moreno Aspitia [j], Henry Gomez [k], Andrea Gombos [c], Maria A. Coccia-Portugal [l], Ling-Ming Tseng [m], Georg Kunz [n], Guillermo Lerzo [o], Joohyuk Sohn [p], Vladimir Semiglazov [q], Cristina Saura [a], Judith Kroep [r], Antonella Ferro [s], David Cameron [t], Richard Gelber [u], Jens Huober [v,l], Serena Di Cosimo [w,l]

[a] *Vall d'Hebron Institute of Oncology, Barcelona Spain. SOLTI, Barcelona, Spain*
[b] *Frontier Science (Scotland) Ltd, Kincraig, Kingussie, UK*
[c] *Institut Jules Bordet, Université Libre de Bruxelles (ULB) Brussels, Belgium*
[d] *Global Drug Development, Novartis, Basel, Switzerland*
[e] *Breast International Group, Brussels, Belgium*
[f] *Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil*
[g] *The Institute of Cancer Research ICR-CTSU, London, UK*
[h] *Dept. of Medicine II, Hematology & Oncology University of Frankfurt, Frankfurt, Germany*
[i] *Division of Medical Senology, IEO, European Institute of Oncology, IRCCS, Milan, Italy*
[j] *Jacoby Center for Breast Health, Mayo Clinic, Jacksonville, FL, USA*
[k] *National Institute of Neoplastic Diseases Ricardo Palma University Lima, Peru*
[l] *Coccia-Portugal M, Eastleigh Breast Care Centre, Pretoria, South Africa*
[m] *Taipei-Veterans General Hospital, National Yang Ming Chiao Tung University, Taipei, Taiwan*
[n] *Dept. Obstet./Gyn., St.-Johannes-Hospital, Dortmund, Germany*
[o] *Fundación CENIT Para La Investigación Ciudad Autónoma de Buenos Aires, Argentina*
[p] *Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*
[q] *Breast Cancer Department, N.N. Petrov National Medical Research Center of Oncology, St. Petersburg, Russian Federation*
[r] *Department Medical Oncology, Leiden University Medical Center, Leiden, The Netherlands. Dutch Breast Cancer Oncology Group (BOOG), the Netherlands*
[s] *Department of Medical Oncology, Rete Clinica Senologica- Santa Chiara Hospital, Trento, Italy*
[t] *Edinburgh Cancer Research, The University of Edinburgh, Institute of Genetics and Cancer, Crewe Road South, Edinburgh, UK*

* *Corresponding author*: Vall d'Hebron University Hospital Vall d'Hebron Institute of Oncology (VHIO) CENTRE CELLEX C/ Natzaret, 115-117 08035 Barcelona, Spain. www.vhio.net.
E-mail address: pnuciforo@vhio.net (P. Nuciforo).
[1] co-last authors.

https://doi.org/10.1016/j.ejca.2022.12.020

[u] Department of Data Science, Dana-Farber Cancer Institute, Harvard Medical School, Harvard TH Chan School of Public Health, Frontier Science Foundation, Boston, MA, USA
[v] Cantonal Hospital St.Gallen | Breast Center | St.Gallen, Switzerland. University of Ulm, Breast Center, Ulm, Germany
[w] Integrated Biology Platform, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Received 7 November 2022; received in revised form 20 December 2022; accepted 20 December 2022
Available online 27 December 2022

KEYWORDS
Breast cancer;
HER2-Positive;
Neoadjuvant;
Pathological complete response;
Long-term survival;
Dual anti-HER2 blockade

Abstract ***Background:*** Dual anti-HER2-targeted therapy in breast cancer (BC) significantly increased the rate of pathological complete response (pCR) compared to single blockade when added to chemotherapy. However, limited data exist on the long-term impact on survival of the additional increase in pCR.
Methods: Neoadjuvant lapatinib and/or trastuzumab treatment optimisation (NCT00553358) is an international, randomised, open-label, phase III study investigating the addition of lapatinib to chemotherapy plus trastuzumab in HER2-positive early BC. Ten-year event-free survival (EFS), overall survival (OS) and safety were assessed on intention-to-treat population. The association between pCR and EFS or OS was investigated in landmark population.
Results: A total of 455 patients were randomised to receive lapatinib (154), trastuzumab (149) or the combination (152). Ten-year EFS estimates were 63% (95% confidence interval [CI], 54%–71%) in the lapatinib group, 64% (95% CI, 55%–72%) in the trastuzumab group and 67% (95% CI, 58%–74%) in the combination group. Ten-year OS rates were 76% (95% CI, 67%–83%), 75% (95% CI, 66%–82%) and 80% (95% CI, 73%–86%) in the lapatinib, trastuzumab and combination groups, respectively. Women who achieved a pCR had improved EFS (hazard ratio 0.48, 95% CI, 0.31–0.73) and OS (hazard ratio 0.37, 95% CI, 0.20–0.63) compared with those who did not. The numerical difference in survival according to pCR status was greater in women treated with the combination and those with hormone-receptor-negative tumours. There were no new or long-term safety concerns.
Conclusions: Patients with HER2-positive BC showed a durable survival benefit of neoadjuvant anti-HER2, irrespective of treatment arm. Patients who achieve pCR have significantly better outcomes than patients without pCR.

1. Introduction

For primary resectable HER2-positive breast cancer, neoadjuvant therapy has become a routine treatment, with trastuzumab representing the first HER2-targeted agent. Dual anti-HER2 blockades, with other agents including lapatinib and pertuzumab, achieved a higher pathological complete response (pCR) rate than single agent trastuzumab-based strategy [1–4]; however, the ability of neoadjuvant dual-blockade to produce significant long-term clinical improvement remains somewhat controversial.

The primary analysis of neoadjuvant lapatinib and/or trastuzumab treatment optimisation (NeoALTTO) study showed that patients with early-stage HER2-positive breast cancer, who received neoadjuvant dual anti-HER2 inhibition with lapatinib and trastuzumab plus weekly paclitaxel, had a significant improvement in pCR in the breast by approximately 20% compared to either treatment alone [1]. In prespecified secondary end-point analyses conducted after a median follow-up of 3.8 years and 6.7 years, patients achieving a pCR had a significantly better event-free survival (EFS) (3-year rates of 86% versus 72%; 6-year rates of 77% versus 65%) and overall survival (OS) (3-year rates of 94% versus 87%; 6-year rates of 89% versus 77%) compared with those without a pCR. However, EFS and OS did not significantly differ between treatment groups [5,6].

Here, we report the final pre-planned 10-years survival analysis of NeoALTTO and the association between pCR and survival outcomes.

2. Methods

2.1. Study design and participants

The study design was previously reported [1,5,6]. Briefly, NeoALTTO was a phase III, multicentre, international study enrolling 455 women who were randomly assigned to receive lapatinib, trastuzumab or the combination of

both drugs. Eligible patients had histologically confirmed HER2-positive early-stage breast cancer, with a tumour size greater than 2 cm, adequate hepatic, renal, cardiac and bone marrow functions at baseline and left ventricular ejection fraction at baseline of 50% or more. HER2 status was assessed centrally (by Vall D'Hebron Institute of Oncology, Barcelona, Spain) or locally (after central laboratory accreditation); hormone receptor status was considered positive or negative as per local guidelines. Women with bilateral, inflammatory or metastatic breast cancer were excluded. The study protocol was approved by ethics committee and relevant health authorities at each participating institution and country. All patients provided written informed consent prior to study entry. The trial protocol is available in Supplementary Material.

2.2. Study procedure

Treatment allocation was by stratified, permuted blocks. With a block size of six, patients were randomly assigned to the three treatments in a 2:2:2 ratio. Stratification factors were hormone receptor status (oestrogen-receptor or progesterone-receptor positive or both versus both oestrogen-receptor and progesterone-receptor negative), clinical nodal involvement (N0–1 versus ≥N2), clinical tumour size (T2 versus ≥T3) and suitability for breast-conserving surgery (yes versus no). In the neoadjuvant phase, patients received oral lapatinib (1500 mg/day), intravenous weekly trastuzumab (4 mg/kg loading dose followed by 2 mg/kg) or a combination of lapatinib (1000 mg/day) plus trastuzumab (the same dose as for single agent) for 6 weeks. After that, patients were given additional weekly paclitaxel (80 mg/m2) for a further 12 weeks. Definitive surgery was done 4 weeks after the last dose of paclitaxel. Adjuvant chemotherapy was given to all patients within 6 weeks of definitive surgery and consisted of three cycles of fluorouracil, epirubicin and cyclophosphamide (FEC) given intravenously every 3 weeks. After chemotherapy, all women received the same anti-HER2 therapy as previously randomly assigned for an additional 34 weeks. Radiotherapy given concomitantly with anti-HER2 drugs was mandatory in women treated with breast-conserving surgery. Radiotherapy was given according to the local guidelines in case of mastectomy and started 4 weeks after the completion of FEC. Endocrine therapy was prescribed for women with hormone-receptor positive tumours as per local policy for a minimum duration of 5 years. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 [1].

2.3. Outcomes

The primary end-point of breast-only pCR (ypT0/is) and secondary end-points including locoregional pCR (ypT0/is ypN0), 3-years and 6-years EFS and OS, safety and tolerability were previously reported [1,5,6]. Here, we report the 10-years EFS and OS estimates as well as updated safety data. EFS was defined as the time from randomisation to the first event (breast cancer relapse after surgery, second primary malignancy or death without recurrence). OS was defined as the time from randomisation to death from any cause. For women who did not undergo breast cancer surgery (n = 28), events were death during clinical follow-up or non-completion of any neoadjuvant investigational product because of disease progression.

Table 1
Study participants included in the intention-to-treat and landmark populations for event-free and overall survival.

	Lapatinib plus trastuzumab	Lapatinib	Trastuzumab	Overall
ITT population	152	154	149	455
Included in EFS landmark analysis	138 (91%)	134 (87%)	138 (93%)	410 (90%)
Excluded from EFS landmark analysis				
EFS event prior to landmark date	2 (1%)	3 (2%)	1 (1%)	6 (1%)
Clinical follow-up ended prior to landmark date	5 (3%)	13 (8%)	7 (5%)	25 (5%)
pCR status unknown at landmark date	7 (5%)	4 (3%)	3 (2%)	14 (3%)
Included in OS landmark analysis	139 (91%)	139 (90%)	142 (95%)	420 (92%)
Excluded from OS landmark analysis				
Death prior to landmark date	1 (1%)	1 (1%)	0 (0%)	2 (<1%)
Survival follow-up ended prior to landmark date	5 (3%)	10 (6%)	4 (3%)	19 (4%)
pCR status unknown at landmark date	7 (5%)	4 (3%)	3 (2%)	14 (3%)

EFS, Event-free survival; OS, Overall survival. The landmark date was 30 weeks after randomisation.

2.4. Statistical analysis

NeoALTTO trial was not powered to detect treatment differences for secondary and post-hoc exploratory end-points. Results of these analyses are for descriptive purposes. All patients in the intention-to-treat (ITT) population were included in EFS and OS analyses. Ten-year survival rates (since randomisation) in the ITT population were obtained with the Kaplan–Meier method. Cox proportional hazards regression model was used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) with *P*-values from two-sided log-rank tests.

Association between pCR and survival end-points were tested using landmark time analyses to adjust for guarantee-time bias [7]. Patients with at least 30-weeks survival from randomisation and known pCR status

were included (Table 1). EFS and OS rates for the landmark analyses are reported using time since the landmark date.

Additional post-hoc exploratory analyses were also carried out. A Cox model was used to test for the effects of baseline clinical factors on EFS in the ITT population. Further Cox models were used to test interactions between pCR and each of the clinical factors individually (adjusted for treatment arm). To investigate changes in hazard rates over time, a life table approach was used to estimate the hazards in subgroups defined by arm, pCR status and hormone receptor status, within the time periods 0–1, 1–2, 2–5 and 5–10 years. The periods were chosen to include sufficient events within each period. Analyses were performed with Statistical Analysis System (SAS) (version 9.4).

3. Results

The NeoALTTO study enrolled 455 patients which were randomly assigned to three treatments groups: 154 (34%) to the lapatinib group, 149 (33%) to the trastuzumab group and 152 (33%) to the combination group. Patient baseline characteristics have been previously reported (Supplementary Table 1) [1]. Median follow-up was 9.7 years (interquartile range, 6.6–9.9 years).

Ten years after the inclusion of the last patients, 137 of 455 patients (30%) had experienced an event, 47 (31%) in the lapatinib group, 47 (32%) in the trastuzumab group and 43 (28%) in the combination group. Since last follow-up analysis at 6.7 years, 10 additional events were observed (Table 2), 3 in the lapatinib group, 2 in the trastuzumab group and 5 in the combination group. Seven of the 10 events were in HR-positive tumours, including the 2 distant bone metastases. The two new second primary (non-breast) malignancies occurred in the uterus and brain. Ten-year EFS rates were 63% (95% CI, 54%–71%) in the lapatinib, 64% (95% CI, 55%–72%) in the trastuzumab and 67% (95% CI, 58%–74%) in the combination group (Fig. 1A). 10-year EFS did not significantly differ between those patients in the lapatinib group and the trastuzumab group (HR 1.01, 95% CI 0.66–1.52, $P = 0.98$) or for those in the combination group compared with trastuzumab alone (HR 0.88, 95% CI 0.57–1.34, $P = 0.55$). Thirty-one patients (20%) in the lapatinib group, 32 (21%) in the trastuzumab group and 26 (17%) in the combination group had died. The 10-year OS rates were 76% (95% CI, 67%–83%), 75% (95% CI, 66%–82%) and 80% (95% CI, 73%–86%) in the lapatinib, trastuzumab and combination groups, respectively. No significant differences in OS were observed between lapatinib and trastuzumab (HR 0.96, 95% CI 0.58–1.60, $P = 0.88$) or between combination and trastuzumab single agent (HR 0.79, 95% CI 0.46–1.34, p = 0.38) (Fig. 1B). There were no significant differences between treatment groups when EFS and OS were analysed by hormone receptor status (Supplementary Fig. 1).

Table 2
Primary type and location of first EFS events.

	Lapatinib plus trastuzumab	Lapatinib	Trastuzumab	Overall
	(N = 152)	(N = 154)	(N = 149)	(N = 455)
Number of patients with EFS events	43 (28%) [38]	47 (31%) [44]	47 (32%) [45]	137 (30%) [127]
CNS recurrence	9 (6%) [9]	6 (4%) [6]	8 (5%) [8]	23 (5%) [23]
Distant visceral recurrence	4 (3%) [4]	15 (10%) [15]	11 (7%) [10]	30 (7%) [29]
Distant bone recurrence	4 (3%) [3]	8 (5%) [7]	5 (3%) [5]	17 (4%) [15]
Other distant recurrence (assumed soft tissue)	3 (2%) [2]	1 (<1%) [1]	4 (3%) [4]	8 (2%) [7]
Regional recurrence	2 (1%) [2]	3 (2%) [2]	0 (0%) [0]	5 (1%) [4]
Local recurrence	9 (6%) [9]	6 (4%) [6]	5 (3%) [5]	20 (4%) [20]
Invasive contralateral breast cancer	4 (3%) [3]	0 (0%) [0]	6 (4%) [5]	10 (2%) [8]
Invasive SPM in ipsilateral breast	0 (0%) [0]	0 (0%) [0]	1 (<1%) [1]	1 (<1%) [1]
Second (non-breast) primary malignancy	4 (3%) [3]	4 (3%) [3]	4 (3%) [4]	12 (3%) [10]
Progression or SPM/CBC during neoadjuvant treatment	1 (<1%) [1]	1 (<1%) [1]	1 (<1%) [1]	3 (<1%) [3]
Death during clinical follow-up (post-surgery)	2 (1%) [1]	2 (1%) [2]	1 (<1%) [1]	5 (1%) [4]
Death during clinical follow-up (no surgery)	1 (<1%) [1]	1 (<1%) [1]	1 (<1%) [1]	3 (<1%) [3]

The number of events recorded at the previous analysis (median 6.7 years follow-up) are shown in square brackets. EFS - Event-free survival. SPM - Second primary malignancy. CBC - Contralateral breast cancer. All EFS events within 60 days were considered simultaneous. The primary type was determined according to a pre-defined hierarchy, shown by the order that the event types are presented in this table. If patients had a simultaneous EFS event of a type lower down the table, this is not shown in the above counts.

Achievement of a pCR was associated with better outcomes. Patients with a pCR had significantly higher EFS (77% versus 61%) and OS (88% versus 72%) 9 years after the landmark date than those who did not (EFS, HR 0.48, 95% CI 0.31–0.73, $P < 0.001$; OS, HR 0.37, 95% CI 0.20–0.63, $P < 0.001$) (Fig. 2A and B). These associations were numerically greater in patients with hormone receptor-negative (EFS, HR 0.43, 95% CI

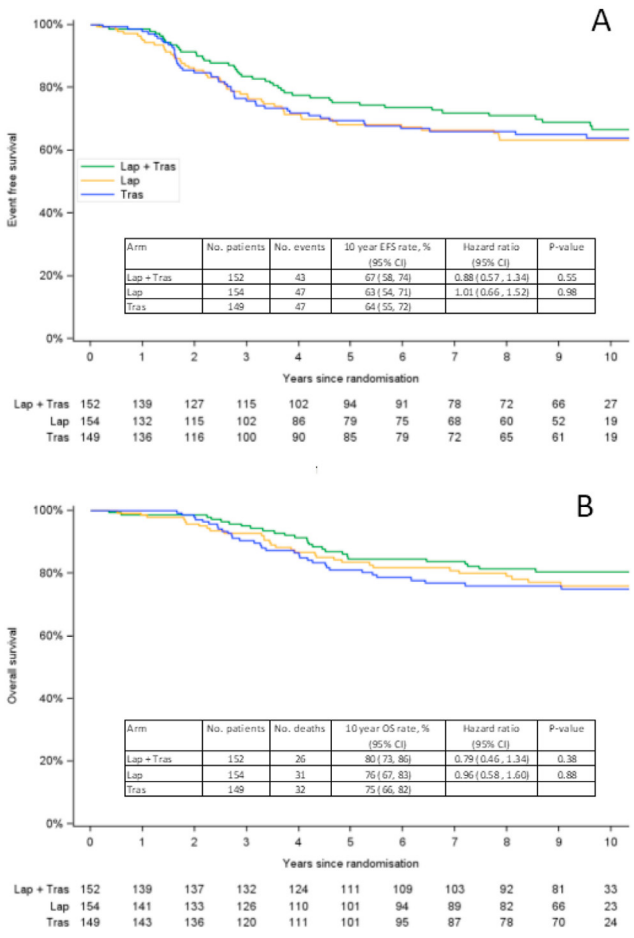

Fig. 1. Event-free survival (**a**) and overall survival (**b**) by treatment group in the ITT population. The number of patients at risk at each time point is shown below the graphs. ITT, intention-to-treat; Lap, lapatinib; Tras, trastuzumab.

0.25–0.73, $P = 0.002$; OS, HR 0.33, 95% CI 0.15–0.66, $P = 0.002$) versus hormone-receptor-positive tumours (EFS, HR 0.60, 95% CI 0.28–1.17, $P = 0.15$; OS, HR 0.44, 95% CI 0.15–1.07, $P = 0.09$) (Fig. 2C and D) and in patients receiving the combination of lapatinib and trastuzumab (EFS, HR 0.35, 95% CI 0.16–0.71, $P = 0.004$; OS, HR 0.22, 95% CI 0.07–0.58, $P = 0.002$) versus trastuzumab alone (EFS, HR 0.60, 95% CI 0.28–1.20, $P = 0.16$; OS, HR 0.41, 95% CI 0.15–1.00, $P = 0.06$) (Fig. 2E and F).

Plotting hazard rates over time revealed that the risk of recurrence increased with a peak up to 2 years after surgery and decreased gradually thereafter to approximately half the peak rate for the time period of 2–5 years with a decreasing trend beyond 5 years. Having a pCR decreased the risk of recurrence compared to non-pCR. At the time period of 1–2 years, the hazard rate of recurrence of patients achieving a pCR (hazard rate = 0.073) was almost half the value of those who did not (hazard rate = 0.121). More importantly, the benefit derived from achieving a pCR was durable as shown by hazard rate over time (Fig. 3). Although the hazard rate for patients without a pCR decreased gradually with time, it remained higher than those with pCR even within the time periods of 5–10 years from surgery. Results were consistent for hormone-receptor-negative- and –positive-disease.

Exploratory subgroup analyses showed that none of the baseline clinical factors tested were significantly associated with EFS in the ITT population (Supplementary Table 2). A similar effect on EFS of having a pCR was observed across clinical subgroups (Supplementary Fig. 2).

Adverse events were assessed in 448 women who received at least one dose of study drug. Since the analysis at median 6.7 years follow-up, there were no further fatal adverse events or non-fatal serious adverse events. Similarly, there have been no further primary or secondary cardiac events recorded since the last analysis.

4. Discussion

The long-term follow-up of the NeoALTTO trial showed a durable survival benefit of neoadjuvant anti-HER2 in patients with early-stage HER2-positive breast cancer. The degree of benefit was similar among patients receiving dual versus single agent anti-HER2 therapies and hormone-receptor positive- versus -negative tumours. However, still approximately, 35% and 25% of women remained at risk of relapse and death at 10 years, respectively, which represents an unmet clinical need to improve outcomes in this population. The peak of events is achieved early with 77% of relapses observed at year 3 [5] while disease relapses after year 6 were infrequent (7%). The results are in line with the long-term outcome and relapse patterns of adjuvant studies with trastuzumab [8].

Importantly, women achieving a pCR after neoadjuvant anti-HER2 therapy had significantly better EFS and OS than women without pCR. The risk of relapse within 9 years from the landmark date was reduced by 41% and the risk to die by 57% in patients with a pCR as compared with patients with residual invasive disease after surgery.

Previous meta-analysis, in which the NeoALTTO study was included, indicated that pCR is likely to predict survival benefit in patients with early-stage *HER2*-positive breast cancer, representing an early patient-level surrogate biomarker of outcome [9–11].However, to what extent pCR may be used as a surrogate biomarker of long-term outcome remains somewhat controversial as most neoadjuvant trials are powered to detect differences in pCR rate among regimens but not powered for long-term outcomes due to several reasons. To our knowledge, with a follow-up of approximately 10 years, NeoALTTO is the largest randomised neoadjuvant study to show that achieving pCR is highly and significantly associated

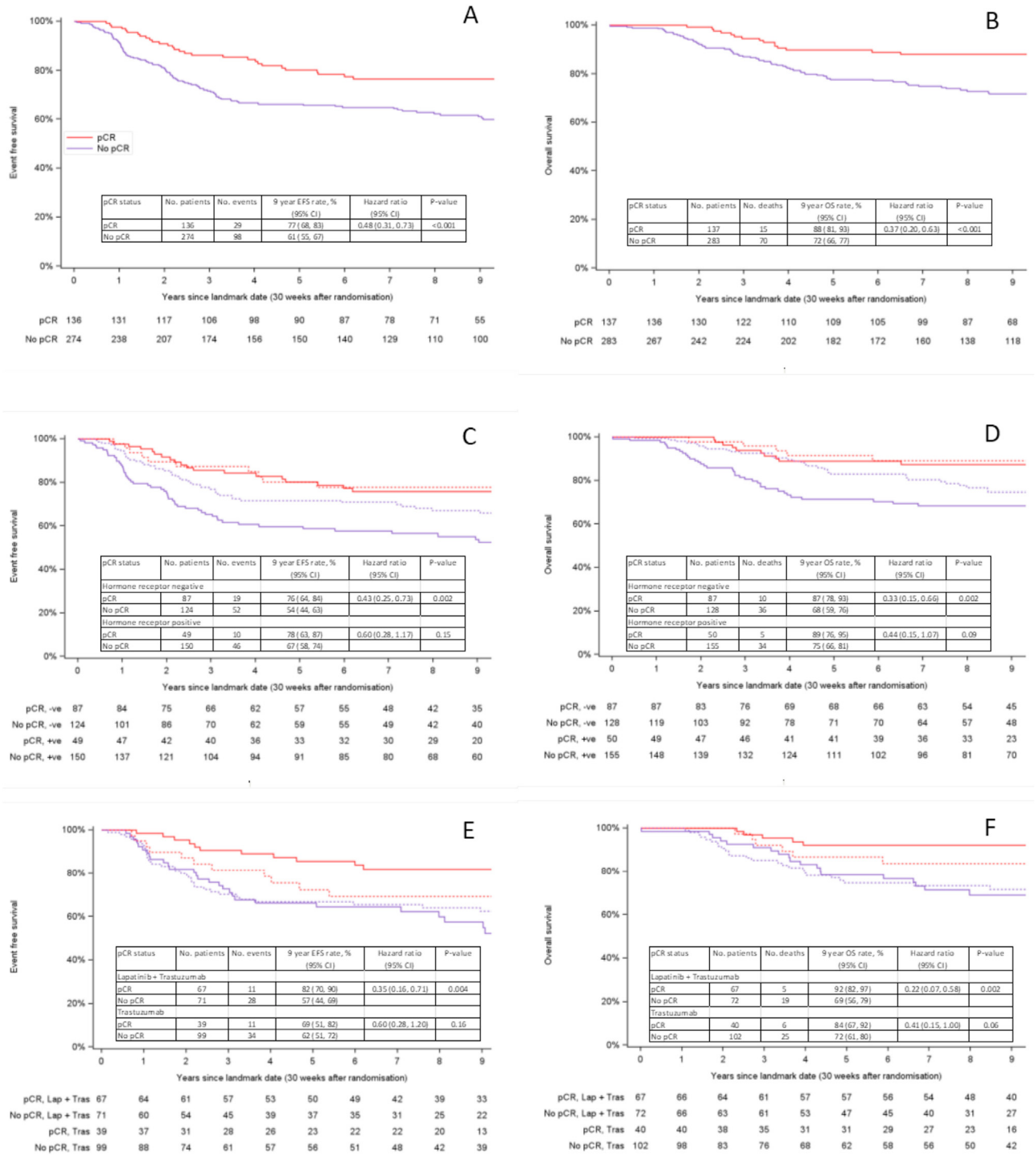

Fig. 2. Event-free survival (**a**), (**c**), (**e**) and overall survival (**b**), (**d**), (**f**) by pCR status in the landmark populations. Patients by hormone receptor status (c), (d) and by treatment arm (e), (f). In figures C and D, solid lines represent patients with hormone-receptor-negative, dashed lines represent patients with hormone-receptor positive. In figures E and F, solid lines represent Lap + Tras, dashed lines represent Tras alone (Lap alone not shown). The number of patients at risk at each time point is shown below the graphs. Lap, lapatinib; pCR, pathological complete response; Tras, trastuzumab, +ve − hormone-receptor positive, -ve − hormone-receptor-negative.
Fig C: p-value = 0.33 for interaction of pCR and HR. Fig D: p-value = 0.63 for interaction of pCR and HR. Fig E: p-value = 0.22 for interaction of Lap + Tras vs Tras x pCR, p-value = 0.71 for interaction of Lap + Tras vs Tras x pCR. Fig F: p-value = 0.43 for interaction of Lap + Tras vs Tras x pCR, p-value = 0.97 for interaction of Lap + Tras vs Tras x pCR.

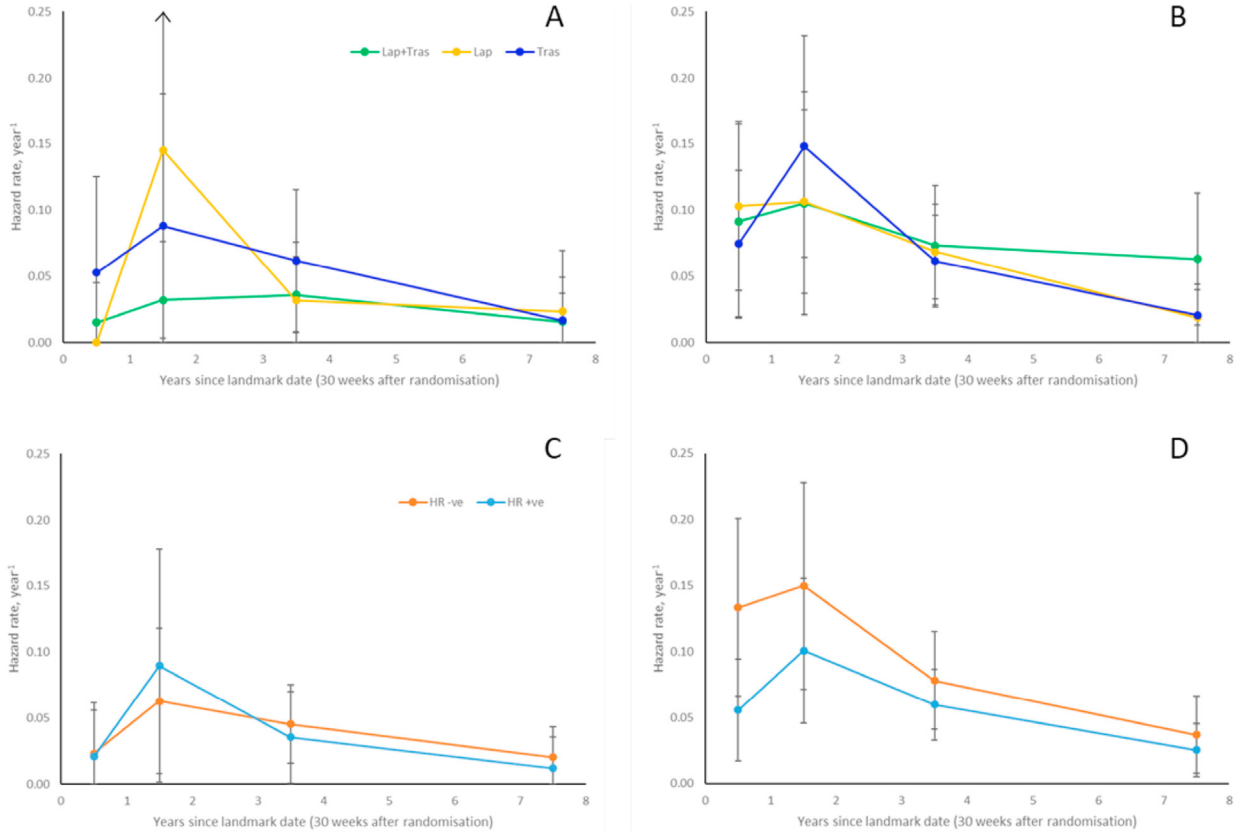

Fig. 3. Hazard rates for event-free survival over time. Patients with pathological complete response (pCR) (**a**), (**c**) and without pCR (**b**), (**d**) at the landmark date. Hazard rates are shown for each treatment arm (a), (b) and for each hormone receptor status group (c), (d). 95% confidence intervals are shown. Lap, lapatinib; Tras, trastuzumab; HR -ve, hormone-receptor-negative; HR + ve, hormone-receptor positive.

with long-term survival. The prognostic impact of pCR was consistent across clinical subgroups.

The NeoALTTO trial showed that the disease-control for the pCR group was durable as illustrated by hazard rates over time. Importantly, the effect on the survival of the additional increase in pCR achieved with a second anti-HER2 agent was seen early and sustained long-term as shown by the absence of late relapses in patients achieving a pCR. The numerically greater benefit found in the combination arm (25% difference in EFS in favour of patients with pCR) than the mono-therapy arms may be explained by the higher sensitivity of HER2-addicted cancers to dual HER2 blockade [12]. This is supported by the correlation between increasing HER2 protein expression and increased benefit of adding lapatinib to trastuzumab observed in the NeoALTTO study [13].

Long-term follow-up is also particularly important for capturing the therapy benefit in patients with hormone-receptor-positive HER2-positive breast cancer. The survival benefit of achieving a pCR was numerically higher for patients with hormone-receptor-negative tumours than those with hormone-receptor-positive disease. This finding is in line with previous reports and supports the notion that hormone-receptor-negative and hormone-receptor-positive HER2-positive breast cancers are two distinct biological entities [2,3,9–11,14].

Post-hoc exploratory multivariable Cox regression analysis did not find any of the baseline clinicopathological factors was predictive of better EFS, strengthening a need for a better understanding of the influence and interconnection of tumour cell features, immune infiltration and clinical parameters on both pCR and survival outcomes to derive better prognostic tools to design future escalation and de-escalation trials in HER2-positive breast cancer. In NeoALTTO, tumour infiltrating lymphocytes and immune signatures seemed to predict higher pCR, whereas only tumour infiltrating lymphocytes were associated with statistically significant better EFS [15,16]. This is in line with the findings of the Cher-LOB trial [4] and supported by a pooled analysis of 3771 breast cancer patients, including 1379 HER2-positive tumours [17].

Although the NeoALTTO trial was not powered to detect significant differences in survival outcomes across treatment arms, a numerical increase in long-term survival rates with dual HER2-targeting was observed,

especially in the hormone-receptor-negative group. This is consistent with a trend towards improved survival with the combination of lapatinib plus trastuzumab over single HER2 blockade observed in other studies [3,4,18]. In the CALGB 40601 phase III trial, a significant improvement in the 7-year RFS and OS was reported with lapatinib plus trastuzumab compared with the trastuzumab single agent [19]. However, the statistically significant effect of dual therapy on relapse and survival should be considered in the context of its secondary analytic nature and, therefore, interpreted with caution also considering the results of the large ALTTO trial which showed only a modest, non-significant, increase in disease-free survival adding lapatinib to trastuzumab (HR = 0.84, $p = 0.048$) [20].

One limitation of the present analyses is that the study was not powered to detect differences in EFS and OS between the three treatment arms; these results are, therefore, descriptive. Moreover, the pCR survival benefit in this high-risk population will need to be confirmed in additional cohorts with long-term follow-up and potentially with dual regimens combining trastuzumab with pertuzumab or other agents.

In conclusion, the long-term follow-up analysis of the NeoALTTO trial shows that among patients who survived 6 years without recurrence, more than 97% of patients survived without additional recurrence or death, regardless of their hormone-receptor status or treatment arm. Patients who achieve pCR have significantly better outcomes than patients without pCR. We acknowledge that the combination studied in NeoALTTO was associated with toxicity and is not utilised in clinical practice based on failure of ALTTO to demonstrate statistically significant benefit (at the $p < 0.025$ level) in the adjuvant setting. However, not only was the combination superior to induce more pCRs (as previously demonstrated as primary end-point) but also this long-term updated analysis of NeoALTTO demonstrated that achieving a pCR by combination anti-HER2 treatment was associated with sustained recurrence-free survival. The present results strengthen pCR as long-term predictor of favourable patient outcome in HER2-positive breast cancer and may have an impact on new trial design testing de-escalation/escalation strategy.

Author contributions

Conceptualisation: PN, MP, EDA, VM, CS, DC, RG, JH, SDC. Investigation, methodology, and/or resources: MP, PG, SA, EDA, GW, VM, MC, HG, AG, MCP, LT, GK, GL, JS, VS, CS, JK, RG, JH, SDC. Formal analysis: PN, JT, SF, RG. Writing-original draft: PN, JT, SF, EDA, GW, SA, JB, RG, JH, SDC. Writing—review & editing: All authors. Supervision: MP, GW, JB, VM, MC, AMA, CS, JK, AF, DC, RG, JH, SDC.

Funding

The NEOALTTO trial was funded and sponsored by GlaxoSmithKline (GSK) and Novartis. NEOALTTO was conducted by the Breast International Group (BIG), Institute Jules Bordet (IJB), GSK/Novartis and SOLTI, and funders imposed no restriction on the investigator in respect to the design and conduct of the study; collection, management, analysis, interpretation of the data, and writing of the report. Statistical analyses were conducted by Frontier Science Scotland. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Prior presentations

Results of this analysis have been partially presented at the European Breast Cancer Congress (EBCC), 8–9 of October, 2020.

Data availability

The data generated and analyzed during this study can be made available upon reasonable request to the corresponding author.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PN reported consulting fees from Novartis, Bayer and MSD Oncology, Novartis, and Targos Molecular Pathology. JT reported salary support funding to the institution from Novartis to act as an independent not-for-profit organisation to undertake the statistical analysis for this study. MP served as Board Member (Scientific Board) for Oncolytics; reported consultant honoraria from AstraZeneca, CamelIDS/Precirix, Gilead, Immunomedics, Lilly, Menarini, MSD, Novartis, Odonate, Pfizer, Roche-Genentech, Seattle Genetics, Immutep, Seagen, NBE Therapeutics, Frame Therapeutics; reported research grants to my Institute from AstraZeneca, Immunomedics, Lilly, Menarini, MSD, Novartis, Pfizer, Radius, Roche-Genentech, Servier, Synthon. SF reported salary support funding to the institution from Novartis to act as an independent not-for-profit organisation to undertake the statistical analysis for this study. PG reported being a Novartis employee. SA reported grant to the institution from Novartis in the context of this work and grants from Roche/Genentech and Pfizer outside the submitted work. EDA reported honoraria and advisory board from Roche/GNE, Novartis, Seattle Genetics, Zodiacs, Lilly, Libbs and Pierre Fabre; travel grants from Roche/GNE, GSK/Novartis; research grant for his

institute from Roche/GNE, Astra-Zeneca, Novartis, and Servier. GW had nothing to disclose. JB reported salary support funding to the institution from Clovis Oncology, Roche, Novartis (previously GSK), Janssen-Cilag, Pfizer, Eli Lilly, AstraZeneca, Merck Sharp & Dohme, Puma Biotechnology. VM had nothing to disclose. MC reported Research Grant from Roche. AMA reported institutional research funds from Genentech, GSK/Novartis and Sermonix. HG reported fees from BMS, Roche, MSD, Novartis, Abbott, Tencofarma. AG reported Advisory Board role for Astra Zeneca/Daiichi Sankyo, Seattle Genetics; grants for conference participation: Pfizer. MCP had nothing to disclose. LT had nothing to disclose. GK had nothing to disclose. GL reported Advisory Board role for Novartis, Pfizer, Roche, Lilly, MSD, GSK. JS reports research funding from MSD, Roche, Novartis, AstraZeneca, Lilly, Pfizer, GSK, Daiichi Sankyo, Sanofi, Boehringer Ingelheim. VS has nothing to disclose. CS served as consultant, participated in advisory boards or received travel grants from AstraZeneca, AX'Consulting, Byondis B.V., Daiichi Sankyo, Eisai, Exact Sciences, Exeter Pharma, F. Hoffmann - La Roche Ltd, ISSECAM, MediTech, Merck Sharp & Dohme, Novartis, Pfizer, Philips, Piere Fabre, PintPharma, Puma, Roche Farma, SeaGen, and Zymeworks, Gilead; grants paid directly to her Institution: Aragon Pharmaceuticals, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb (BMS), Cytomx therapeutics, Daiichi Sankyo, F. Hoffmann-la Roche, Genentech, German Breast Group, Glaxosmithkline, Innoup Farma, International Breast Cancer Study Group (IBCSG), Lilly, Macrogenics, Medica Scientia Innovation, Menarini, Merus, Millennium Pharmaceuticals, Novartis, Pfizer, Puma biotechnology, Queen Mary, University of London, Roche, Sanofi-Aventis, Seattle Genetics, Solti and The Netherlands Cancer Institute-Antoni van Leeuwenhoek Ziekenhuis. JK had nothing to disclose. AF reported speaker honoraria from Eli Lilly, Novartis, Roche and Pfizer. DC reported fees from Aptitude Health, Roche Sweden, Pfizer Limited, Celldex Therapeutics Inc, Carnall Farrar, San Antonio Breast Cancer Consortium, Highfield Communication, Astrazeneca Global Commercial Organisation – Egypt, Celgene Corporation, Chief Scientists Office, Cancer Research UK, HTA, Samsung Bioepis Co Ltd (Korea), ELI LILLY & Company, Costello Medical Consulting Ltd, prIME Oncology, Astra Zeneca UK Limited, Roche Products Ltd, Novartis Pharma AG, Novartis Pharmaceuticals Corporation, Pfizer Limited, PFS Ltd, Novartis Pharmaceuticals UK Limited, Merck Sharp Dohme Limited, PUMA Biotechnology, Inc., Pfizer Limited, F. Hoffmann-La Roche AG, Clovis Oncology, Breast International Group (BIG), Breast Cancer Institute, Daiichi Sankyo, USA, Eisai, Elsevier Ltd, European Cancer Organisation, Exact Therapeutics, G1 Therapeutics, Galapagos NV, Genentech Inc, GSK (Glaxo SmithKline), ICON Clinical Research, Prima BioMED, RTI Health Solutions, Seattle Genetics, Synthon Biopharmaceuticals BV: note name change to Byondis April 2020, Succinct Medical Communication, Seagen, SANOFI, Sapience Therapeutics Ltd, Bexon/Zymeworks Biopharmaceuticals Inc., Make Seconds Count, NexGen, IQVIA. RG reported grants to the institution from Novartis, Roche, and AstraZeneca for partial support of salary. JH: Research Funding: Celgene, Novartis, Hexal, Lilly. Honoraria: Lilly, Novartis, Roche, Pfizer, AstraZeneca, MSD, Celgene; Eisai, Abbvie, Seagen, Gilead; consulting, advisory relationship with Lilly, Novartis, Roche, Pfizer, Hexal, AstraZeneca, MSD, Celgene, Abbvie, Seagen, Gilead; travel expenses from Roche, Pfizer, Novartis, Celgene, Daiichi. SdC received consulting fees from Pierre-Fabre, IQVIA.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.12.020.

References

[1] Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet 2012; 379(9816):633–40. https://doi.org/10.1016/S0140-6736(11)61847-3.

[2] Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13(1):25–32. https://doi.org/10.1016/S1470-2045(11)70336-9.

[3] Robidoux A, Tang G, Rastogi P, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. Lancet Oncol 2013;14(12):1183–92. https://doi.org/10.1016/S1470-2045(13)70411-X.

[4] Guarneri V, Dieci Mv, Griguolo G, et al. Trastuzumab-lapatinib as neoadjuvant therapy for HER2-positive early breast cancer: survival analyses of the CHER-Lob trial. Eur J Cancer 2021;153: 133–41. https://doi.org/10.1016/j.ejca.2021.05.018.

[5] de Azambuja E, Holmes AP, Piccart-Gebhart M, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. Lancet Oncol 2014;15(10):1137–46. https://doi.org/10.1016/S1470-2045(14)70320-1.

[6] Huober J, Holmes E, Baselga J, et al. Survival outcomes of the NeoALTTO study (BIG 1–06): updated results of a randomised multicenter phase III neoadjuvant clinical trial in patients with HER2-positive primary breast cancer. Eur J Cancer 2019;118: 169–77. https://doi.org/10.1016/j.ejca.2019.04.038.

[7] Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response and other comparisons of time-to-event by outcome variables. J Clin Oncol 2008;26(24):3913–5. https://doi.org/10.1200/JCO.2008.16.1000.

[8] Chumsri S, Li Z, Serie DJ, et al. Incidence of late relapses in patients with HER2-positive breast cancer receiving adjuvant trastuzumab: combined analysis of NCCTG N9831 (alliance) and

NRG Oncology/NSABP B-31. J Clin Oncol 2019;37(35):3425–35. https://doi.org/10.1200/JCO.19.00443.

[9] Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384(9938):164–72. https://doi.org/10.1016/S0140-6736(13)62422-8.

[10] Broglio KR, Quintana M, Foster M, et al. Association of pathologic complete response to neoadjuvant therapy in HER2-positive breast cancer with long-term outcomes. JAMA Oncol 2016;2(6):751. https://doi.org/10.1001/jamaoncol.2015.6113.

[11] Spring LM, Fell G, Arfe A, et al. Pathologic complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: a comprehensive meta-analysis. Clin Cancer Res 2020;26(12):2838–48. https://doi.org/10.1158/1078-0432.CCR-19-3492.

[12] Schettini F, Pascual T, Conte B, et al. HER2-enriched subtype and pathological complete response in HER2-positive breast cancer: a systematic review and meta-analysis. Cancer Treat Rev 2020;84:101965. https://doi.org/10.1016/j.ctrv.2020.101965.

[13] Scaltriti M, Nuciforo P, Bradbury I, et al. High HER2 expression correlates with response to the combination of lapatinib and trastuzumab. Clin Cancer Res 2015;21(3):569–76. https://doi.org/10.1158/1078-0432.CCR-14-1824.

[14] Carey LA, Berry DA, Cirrincione CT, et al. Molecular heterogeneity and response to neoadjuvant human epidermal growth factor receptor 2 targeting in CALGB 40601, a randomized phase III trial of paclitaxel plus trastuzumab with or without lapatinib. J Clin Oncol 2016;34(6):542–9. https://doi.org/10.1200/JCO.2015.62.1268.

[15] Fumagalli D, Venet D, Ignatiadis M, et al. RNA sequencing to predict response to neoadjuvant anti-HER2 therapy. JAMA Oncol 2017;3(2):227. https://doi.org/10.1001/jamaoncol.2016.3824.

[16] Salgado R, Denkert C, Campbell C, et al. Tumor-infiltrating lymphocytes and associations with pathological complete response and event-free survival in HER2-positive early-stage breast cancer treated with lapatinib and trastuzumab. JAMA Oncol 2015;1(4):448. https://doi.org/10.1001/jamaoncol.2015.0830.

[17] Denkert C, von Minckwitz G, Darb-Esfahani S, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. Lancet Oncol 2018;19(1):40–50. https://doi.org/10.1016/S1470-2045(17)30904-X.

[18] Guarneri V, Frassoldati A, Bottini A, et al. Preoperative chemotherapy plus trastuzumab, lapatinib, or both in human epidermal growth factor receptor 2–positive operable breast cancer: results of the randomized phase II CHER-LOB study. J Clin Oncol 2012;30(16):1989–95. https://doi.org/10.1200/JCO.2011.39.0823.

[19] Fernandez-Martinez A, Krop IE, Hillman DW, et al. Survival, pathologic response, and genomics in CALGB 40601 (alliance), a neoadjuvant phase III trial of paclitaxel-trastuzumab with or without lapatinib in HER2-positive breast cancer. J Clin Oncol 2020;38(35):4184–93. https://doi.org/10.1200/JCO.20.01276.

[20] Piccart-Gebhart M, Holmes E, Baselga J, et al. Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2–positive breast cancer: results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. J Clin Oncol 2016;34(10):1034–42. https://doi.org/10.1200/JCO.2015.62.1797.