De-escalated neoadjuvant weekly nab-paclitaxel with trastuzumab and pertuzumab versus docetaxel, carboplatin, trastuzumab, and pertuzumab in patients with HER2-positive early breast cancer (HELEN-006): a multicentre, randomised, phase 3 trial

Xiu-Chun Chen, De-Chuang Jiao, Jiang-Hua Qiao, Cheng-Zheng Wang, Xian-Fu Sun, Zhen-Duo Lu, Lian-Fang Li, Chong-Jian Zhang, Min Yan, Ya Wei, Bo Chen, Yue-Qing Feng, Miao Deng, Ming-De Ma, Jennifer K Plichta, You-Wen He, Zhen-Zhen Liu

Summary

Background A previous phase 2 trial showed promising outcomes for patients with HER2-positive early-stage breast cancer using neoadjuvant de-escalation chemotherapy with paclitaxel, trastuzumab, and pertuzumab. We aimed to evaluate the efficacy of weekly nab-paclitaxel compared with the standard regimen of docetaxel plus carboplatin, both with trastuzumab and pertuzumab, as neoadjuvant therapies for patients with HER2-positive breast cancer.

Methods HELEN-006 was a multicentre, randomised, phase 3 trial done at six hospitals in China. We enrolled patients aged 18–70 years with untreated, histologically confirmed stage II–III invasive HER2-positive breast cancer and an Eastern Cooperative Oncology Group performance status of 0 or 1. Using an interactive response system, patients were randomly assigned (1:1) under a permuted block randomisation scheme (block size of four), stratified by tumour stage, nodal status, and hormone receptor status. Patients received either intravenous nab-paclitaxel (125 mg/m² on days 1, 8, and 15) for six 3-week cycles, or intravenous docetaxel (75 mg/m² on day 1) plus intravenous carboplatin (area under the concentration-time curve 6 mg/mL per min on day 1) for six 3-week cycles. Both groups also received concurrent intravenous trastuzumab, with an initial loading dose of 8 mg/kg and a maintenance dose of 6 mg/kg on day 1, as well as intravenous pertuzumab with a loading dose of 840 mg and a maintenance dose of 420 mg on day 1. This report is the final analysis of the primary endpoint, pathological complete response (ypT0/is ypN0), analysed in all patients who started treatment (modified intention to treat). The trial is registered with ClinicalTrials.gov, NCT04547907, and follow-up of the adjuvant phase is ongoing.

Findings Between Sept 20, 2020, and March 1, 2023, 789 patients were screened for eligibility, 689 of whom were randomly assigned (343 to the nab-paclitaxel group and 346 to the docetaxel plus carboplatin group). All 689 patients were Asian women. 669 patients received at least one dose of the study treatment and were included in the full analysis set (332 in the nab-paclitaxel group and 337 in the docetaxel plus carboplatin group). Median age of the patients was 50 years (IQR 43–55). Median follow-up time was 26 months (IQR 19–32). 220 (66·3% [95% CI 61·2–71·4]) patients in the nab-paclitaxel group had a pathological complete response, compared with 194 (57·6% [52·3–62·9]) in the docetaxel plus carboplatin group (combined odds ratio 1·54 [95% CI 1·10–2·14]; stratified p=0·011). 100 (30%) patients in the nab-paclitaxel group and 128 (38%) in the docetaxel plus carboplatin group had grade 3–4 adverse events. The most common grade 3–4 adverse events were nausea (22 [7%] in the nab-paclitaxel group *vs* 76 [23%] in the docetaxel plus carboplatin group), diarrhoea (25 [8%] *vs* 55 [16%]), and neuropathy (43 [13%] *vs* eight [2%]). Serious drug-related adverse events were reported in three (1%) patients in the nab-paclitaxel group and five (2%) in the docetaxel plus carboplatin group. No treatment-related deaths were reported in either group.

Interpretation These findings might suggest a potential advantage of nab-paclitaxel combined with trastuzumab and pertuzumab compared with the standard regimen in neoadjuvant therapy for patients with HER2-positive early breast cancer, suggesting that this new combination might establish a new standard for neoadjuvant treatment in this patient population.

Funding National Natural Science Foundation of China, and Science and Technology Research Projects of Henan Province, China.

Lancet Oncol 2024

Published Online November 26, 2024 https://doi.org/10.1016/S1470-2045(24)00581-3

For the Chinese translation of the abstract see Online for appendix 1

Department of Breast Disease, Henan Breast Cancer Centre, The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China (X-C Chen MM, D-C Jiao MD, J-H Qiao MD, C-Z Wang MD, X-F Sun MD, Z-D Lu MM, L-F Li MD, C-J Zhang MM, M Yan MD, Z-Z Liu MD); **Department of Breast Surgery, Anyang Tumor Hospital, Anyang, China** (Y Wei MM); **Department of Breast Surgery, The First Hospital of China Medical University, Shenyang, China** (B Chen MD); **Department of Breast Surgery, Xinxiang Central Hospital, Xinxiang, China** (Y-Q Feng MM); **Department of Breast Surgery, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China** (M Deng MM); **Department of Thyroid and Breast Surgery, Huaihe Hospital of Henan University, Kaifeng, China** (M-D Ma MM); **Department of Surgery** (Prof J K Plichta MD) **and Department of Integrative Immunobiology** (Prof Y-W He MD PhD), **Duke University School of Medicine, Durham, NC, USA**

Correspondence to:
Dr Zhen-Zhen Liu, Department of Breast Disease, Henan Breast Cancer Centre, The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou 450008, China
zlyyliuzhenzhen0800@zzu.edu.cn

Research in context

Evidence before this study

We searched PubMed for English-language articles published from database inception to Dec 31, 2019 using the terms "HER2-positive breast cancer", "neoadjuvant therapy", "trastuzumab", "pertuzumab", and "de-escalation". Our review included studies on de-escalation chemotherapy regimens, reporting pathological complete response rates and safety outcomes in patients with early-stage HER2-positive breast cancer. Notably, the 2017 WSG ADAPT HER2+/HR– phase 2 trial showed a pathological complete response rate of up to 91% with 12 weeks of paclitaxel combined with trastuzumab and pertuzumab in patients with HER2-positive and hormone receptor-negative breast cancer, compared with 34% with dual-targeted therapy without chemotherapy. A repeat search on Dec 31, 2023, included the 2021 PHERGain study, which used [^{18}F]fluorodeoxyglucose-PET to identify patients with an early response who could benefit from a chemotherapy-free regimen with trastuzumab and pertuzumab. This study reported a 38% pathological complete response rate, lower than the 58% observed with combined chemotherapy and dual-target therapy. The 2022 WSG ADAPT HER2+/HR study's 5-year follow-up suggested that 12 weeks of weekly paclitaxel plus dual HER2 blockade is an effective de-escalated neoadjuvant regimen in hormone receptor-negative, HER2-positive early breast cancer, with high pathological complete response rates and favourable 5-year outcomes.

Added value of this study

To the best of our knowledge, HELEN-006 is the first multicentre, randomised phase 3 study to show improved pathological complete response rates and fewer adverse events with the combination of single-agent nab-paclitaxel, trastuzumab, and pertuzumab compared with the standard regimen in patients with early HER2-positive breast cancer.

Implications of all the available evidence

Findings from the HELEN-006 trial suggest a potential shift in neoadjuvant treatment practices for patients with HER2-positive early breast cancer, specifically using nab-paclitaxel to reduce treatment-related toxicity without compromising efficacy. This approach seems especially beneficial for hormone receptor-negative patients, who showed significant improvements in pathological complete response rates. Future research should focus on long-term outcomes, such as event-free survival and overall survival, to further validate the clinical benefits of this regimen.

Introduction

HER2 overexpression, observed in 15–20% of patients with breast cancer, is a key predictor of disease recurrence and mortality.[1,2] Targeted therapy plus multiple-agent chemotherapy as first-line regimens for patients with HER2-positive breast cancer have substantially improved survival rates;[3,4] however, the persistently high chemotherapy-related toxicity has prompted exploration of de-escalation strategies, such as chemotherapy-free or reduced-intensity chemotherapy regimens.[5]

Previous studies have investigated the possibility of chemotherapy-free regimens. The PHERGain study[6] and the WSG-ADAPT-HER2+/HR– phase 2 study[7] showed that patients who had an early response to the targeted therapies trastuzumab and pertuzumab, in the absence of chemotherapy, could have a pathological complete response rate of 34–38%. Additionally, the KRISTINE study[8] found that six cycles of trastuzumab emtansine combined with pertuzumab resulted in a pathological complete response rate of 44%. Other biomarker-driven de-escalated studies have also found that patients who have an early response can have meaningful pathological complete response rates, even when chemotherapy is completely omitted.[9,10] However, these pathological complete response rates are still relatively low compared with regimens that include chemotherapy.

A reduced-intensity chemotherapy plus targeted therapy regimen might be a feasible de-escalation strategy. In the neoadjuvant setting, the WSG-ADAPT-HER2+/HR– phase 2 study[7] reported a high pathological complete response rate of 91% with paclitaxel single-agent chemotherapy plus dual HER2 blockade for patients with HER2-positive and hormone-receptor-negative breast cancer. However, the sample size was limited to 42 patients. As such, an additional phase 3 clinical trial with more patients is needed to validate the potential of single-agent taxane chemotherapy in combination with dual targeted therapy for the neoadjuvant treatment of patients with HER2-positive breast cancer.

Nab-paclitaxel, a formulation of paclitaxel bound to albumin without solvents, offers several potential advantages over solvent-based taxanes such as paclitaxel and docetaxel. The benefits include the ability to administer higher doses, shorter infusion times, and increased drug concentrations.[11] The GeparSepto study[12,13] showed that weekly nab-paclitaxel significantly improves the pathological complete response rate in neoadjuvant breast cancer treatment compared with weekly paclitaxel, both followed by epirubicin and cyclophosphamide (38% *vs* 29%; unadjusted p=0·00065). There were numerical increases in pathological complete response and invasive disease-free survival without statistical significance in the HER2-positive subgroup of patients, possibly due to the small sample size limiting the statistical power. Consequently, we adopted a weekly nab-paclitaxel regimen at a dose of 125 mg/m² in the nab-paclitaxel group in this study to investigate its potential superiority, given that non-inferiority had already been met.

We aimed to compare the pathological complete response rates between the de-escalated regimen of

weekly nab-paclitaxel combined with trastuzumab and pertuzumab, and the standard neoadjuvant chemotherapy regimen of docetaxel plus carboplatin with the same dual HER2-targeted therapy in patients with HER2-positive early breast cancer. Here, we report the primary endpoint of pathological complete response, along with safety outcomes.

Methods

Study design and participants

HELEN-006 was a multicentre, randomised, phase 3 study conducted at six hospitals in China (appendix 2 p 1). We enrolled patients aged 18–70 years who had previously untreated, histologically confirmed clinical stage II–III (T1 and N1–3 or T2–4 and N0–3) invasive HER2-positive breast cancer and were eligible for surgery. The tumour staging was conducted according to the American Joint Committee on Cancer staging system.[14] To be eligible, patients had to have an Eastern Cooperative Oncology Group performance status of 0 or 1 and measurable lesions detectable by ultrasound, mammography, or MRI within 1 month before randomisation. Organ and bone marrow function tests had to report an absolute neutrophil count of at least $2{\cdot}0\times10^9$ cells per L, haemoglobin of at least 100 g/L, and platelets of at least 100×10^9 platelets per L. Total bilirubin, creatinine, aspartate aminotransferase, and alanine aminotransferase concentrations needed to be less than 1·5 times the upper limit of normal. Cardiac ultrasound required a left ventricular ejection fraction of at least 55%. Additionally, women of reproductive age needed a negative serum pregnancy test within 14 days before randomisation. Exclusion criteria included patients with bilateral breast cancer, a history of other malignancies except for adequately treated skin cancer, previous systemic therapy for the treatment or prevention of breast cancer, contraindications to the study drugs, or any other reasons the investigators deemed the patients unsuitable for enrolment.

HER2 positivity was determined by HER2 immunohistochemical staining score of 3+ or, if 2+, by *HER2* gene amplification as shown by fluorescence in-situ hybridisation assay. Central laboratory evaluation determined oestrogen receptor, progesterone receptor, and HER2 status. The cutoff value for Ki-67, established by the International Ki-67 in Breast Cancer Working Group,[15] was set at 30%, categorising Ki-67 expression into high and low levels.

Ethics approval was obtained from the ethics committee or institutional review board at each participating site. This trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Before participation, all patients provided written informed consent. This study was registered as an International Standard Randomised Controlled Trial with ClinicalTrials.gov, NCT04547907.

Randomisation and masking

Enrolled patients were randomly assigned (1:1) to receive either nab-paclitaxel, trastuzumab, and pertuzumab or the standard docetaxel, carboplatin, trastuzumab, and pertuzumab regimen using an interactive response system and permuted blocks with a block size of four, ensuring balance between treatment groups across key stratification factors. Although some strata might end with incomplete blocks, overall group balance was maintained. Randomisation was done at the Henan Cancer Hospital (Zhengzhou, China) and was stratified based on tumour stage (T1–2 *vs* T3–4), nodal status (N0 [negative or suspicious imaging with negative biopsy] *vs* N-positive confirmed by biopsy), and hormone receptor status (positive [oestrogen receptor-positive or progesterone receptor-positive] *vs* negative [oestrogen and progesterone receptor-negative). An independent statistician, not involved in the study, generated the random allocation sequence. Clinical investigators at each study site enrolled participants. Study nurses, masked to the allocation sequence, assigned participants to the two treatment groups. Patients with complete baseline documentation were added to the randomisation database, where they were assigned patient numbers and treatment groups. This information was then communicated to participating sites. Neither the patients nor the investigators were masked to the assigned treatments. The central pathologists evaluating the pathological results were masked to the treatment assignments.

Procedures

Patients in the nab-paclitaxel group received intravenous nab-paclitaxel at a dose of 125 mg/m² on days 1, 8, and 15 for six 3-week cycles. Patients in the docetaxel plus carboplatin group received intravenous docetaxel at a dose of 75 mg/m² on day 1, and intravenous carboplatin at a dose based on the area under the concentration-time curve (AUC) of 6 mg/mL per min on day 1 for six 3-week cycles. Both groups also received concurrent intravenous trastuzumab, with an initial loading dose of 8 mg/kg and a maintenance dose of 6 mg/kg on day 1, as well as intravenous pertuzumab with a loading dose of 840 mg and a maintenance dose of 420 mg on day 1 (appendix 2 p 4).

See Online for appendix 2

Adverse events were assessed at each treatment and follow-up visit and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.[16] In case of severe haematological or non-haematological toxic effects, dose reductions or treatment discontinuations were mandatory. Specific recommendations and dose levels were provided for each drug. For nab-paclitaxel, dose levels were defined as level 1 (100 mg/m²) and level 2 (80 mg/m²). For docetaxel, dose levels were defined as level 1 (60 mg/m²) and level 2 (50 mg/m²). For carboplatin, dose levels were defined as level 1

(AUC 5 mg/mL per min) and level 2 (AUC 4 mg/mL per min). No dose reductions were recommended for trastuzumab or pertuzumab, although treatment discontinuation was encouraged in case of severe toxic effects possibly related to these compounds. If toxicity recovered within 3 weeks to grade 1, a restart of treatment could be considered.

The docetaxel plus carboplatin group received standard premedication with dexamethasone to prevent docetaxel-induced hypersensitivity reactions. For this group, the use of pegylated recombinant human granulocyte-colony stimulating factor (G-CSF) was permitted for primary and secondary prophylaxis of treatment-emergent neutropenia. In the nab-paclitaxel group, growth factors such as filgrastim, pegfilgrastim, lenograstim, and others were used for secondary prophylaxis of treatment-emergent neutropenia at the investigator's discretion.

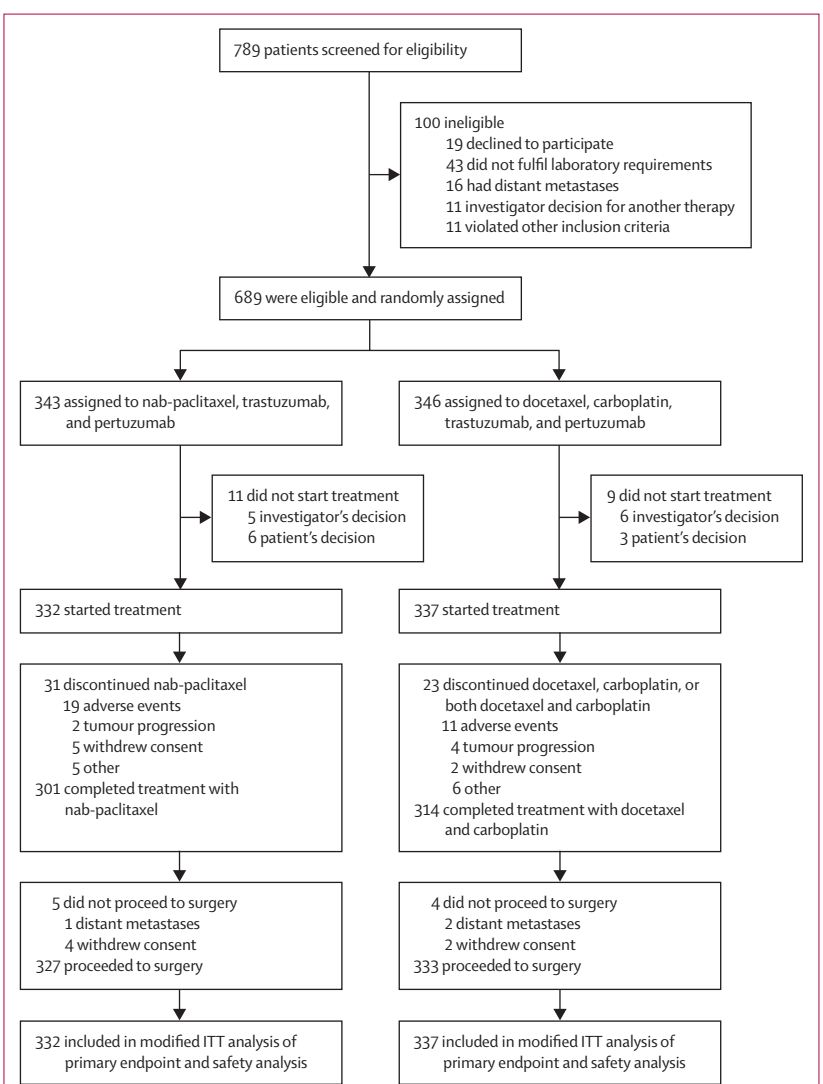

Figure 1: **Trial profile**
ITT=intention to treat.

Treatment continued until one of the following occurred: confirmed disease progression, intolerable toxicity, a decision by the physician, or patient withdrawal, with no allowance for crossover. Patients were followed up for a minimum of 1 month, regardless of continuation of the study treatment, unless consent was withdrawn.

During the screening phase, evaluations of the primary tumour and regional lymph nodes were done using ultrasound, mammography, and physical examination. Subsequently, ultrasounds and physical examinations were performed before each treatment cycle and before surgery, with mammography also conducted before surgery. Additional breast imaging was undertaken at the investigator's discretion. Further investigations, including bone scans, chest radiographs, and liver imaging, were carried out as clinically indicated to rule out metastatic disease. Routine laboratory monitoring, comprising haematological assessments and serum chemistry, was completed before each treatment cycle and surgery. Gender confirmation at baseline was based on the information recorded on the patient's identification card.

After 2–6 weeks from the completion of the last neoadjuvant regimen cycle, participants underwent definitive surgery, which included breast conservation or mastectomy with sentinel lymph-node evaluation or axillary dissection as clinically indicated. Tumour samples were collected and evaluated through a central pathology review. During the adjuvant phase, radiotherapy was administered based on clinical need, and patients with tumours that were positive for oestrogen receptor, progesterone receptor, or both, received adjuvant endocrine therapy. Recommendations for targeted therapy after surgery were based on the National Comprehensive Cancer Network guidelines. Comprehensive details of breast surgery and treatments after surgery are in appendix 2 (p 2).

Outcomes

The primary endpoint was the pathological complete response rate, described as the absence of residual invasive carcinoma in both the resected breast specimen and all sampled ipsilateral axillary lymph nodes (ypT0/is ypN0), as determined centrally in the Henan Cancer Hospital (Zhengzhou, China) by haematoxylin and eosin staining, in accordance with the American Joint Committee on Cancer staging system.[14]

Secondary endpoints were event-free survival (defined as time from randomisation to disease progression during neoadjuvant treatment, disease recurrence, or death from any cause), invasive-disease-free survival (time from surgery to the first documented occurrence of an event such as ipsilateral invasive breast tumour recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause), safety (including the incidence, type, and severity of all adverse events, including serious adverse events based on NCI CTCAE

version 4·0[16]), and tolerability (rates of dose adjustment and discontinuation). Survival data are immature, and secondary survival endpoints will be reported after a longer follow-up.

The prespecified exploratory endpoint compared pathological complete response rates between the nab-paclitaxel and docetaxel plus carboplatin groups across stratification factors (tumour stage, nodal status, and hormone receptor status).

Statistical analysis

The sample size calculation was based on specific assumptions. According to previous studies,[6,8] it was assumed that the overall pathological complete response rate for the docetaxel plus carboplatin group would be 55%. An expected pathological complete response rate of 66% in the nab-paclitaxel group corresponded to an odds ratio (OR) of 1·59. The study was designed as a superiority trial, and a closed test procedure,[17,18] prespecified in the protocol, was used to test for non-inferiority first as a gatekeeper. If non-inferiority was shown, superiority would be tested subsequently. With an assumed 10% dropout rate and 344 patients enrolled in each group, a χ^2 test calculates an 80% power for the two-sided significance level (α) of 0·05 to show the superiority of nab-paclitaxel. For the non-inferiority test, nab-paclitaxel would be considered non-inferior to docetaxel plus carboplatin if the lower 95% CI for the OR was above 0·80, equivalent to a pathological complete response of 49·5% using a non-inferiority margin of 5·5%, since it was believed a pathological complete response rate less than 49·5% would be too low to be considered clinically meaningful in practice.

All patients who started treatment after randomisation were included in the modified intention-to-treat population. Patients who were randomly assigned but did not start assigned treatment were excluded from analyses. Patients without a reported assessment of pathological complete response (eg, those with disease progression or who did not have surgery) were categorised as not having a pathological complete response. The primary efficacy endpoint of the proportion of patients with a pathological complete response was analysed in the modified intention-to-treat population and compared between treatment groups using the Cochran-Mantel-Haenszel χ^2 test (stratified by tumour stage, node status, and hormone receptor status at presentation). In the analysis of exploratory endpoints, the χ^2 test was used to compare pathological complete response rates between treatment groups within each stratification factor. The χ^2 test was also used in post-hoc analyses to compare residual cancer burden results and alternatively defined pathological complete response rates (ypT0 ypN0, ypT0/is ypN0/+, and ypTany ypN0). The interaction effects were assessed using the Wald test.

All statistical analyses were two-sided, and $p<0·05$ was deemed statistically significant. Statistical analyses were done using SPSS version 25.0 and R version 4.2.2.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Nab-paclitaxel, trastuzumab, and pertuzumab group (n=332)	Docetaxel, carboplatin, trastuzumab, and pertuzumab group (n=337)
Median age, years	50 (41–55)	50 (44–56)
Age, years		
≤50	175 (53%)	171 (51%)
>50	157 (47%)	166 (49%)
Women	332 (100%)	337 (100%)
Asian	332 (100%)	337 (100%)
Menopausal status		
Premenopausal	180 (54%)	184 (55%)
Postmenopausal	152 (46%)	153 (45%)
T stage		
T1 to T2	277 (83%)	281 (83%)
T3 to T4	55 (17%)	56 (17%)
Nodal status		
Positive	241 (73%)	247 (73%)
Negative	91 (27%)	90 (27%)
Disease stage		
Stage II	214 (64%)	212 (63%)
Stage III	118 (36%)	125 (37%)
Histological tumour type		
Ductal	315 (95%)	317 (94%)
Lobular	3 (1%)	4 (1%)
Other	14 (4%)	16 (5%)
Tumour grading		
G1	1 (<1%)	1 (<1%)
G2	141 (42%)	142 (42%)
G3	190 (57%)	194 (58%)
Hormone receptor status*		
Positive	196 (59%)	193 (57%)
Negative	136 (41%)	144 (43%)
Ki-67 index		
≤30%	73 (22%)	75 (22%)
>30%	259 (78%)	262 (78%)
HER2 status		
Immunohistochemistry 3+	233 (70%)	233 (69%)
Immunohistochemistry 2+ and ISH-positive	99 (30%)	104 (31%)

Data are median (IQR) or n (%). ISH=in-situ hybridisation. *Oestrogen or progesterone receptor positive is classified as hormone receptor positive; oestrogen and progesterone receptor negative is classified as hormone receptor negative.

Table 1: **Baseline characteristics of the modified intention-to-treat population**

Results

Between Sept 20, 2020, and March 1, 2023, 789 patients were screened for eligibility, 689 of whom were randomly assigned: 343 to the nab-paclitaxel group and 346 to the docetaxel plus carboplatin group. All 689 patients were Asian women. At the end of the enrolment period, simultaneous screening by multiple centres led to one extra patient being enrolled beyond the planned sample size. After consulting with the principal investigator and the statistician, this patient was included in the modified intention-to-treat analyses. 669 patients received at least one dose of the study treatment and were included in the full analysis set (332 in the nab-paclitaxel group and 337 in the docetaxel plus carboplatin group; figure 1). Baseline characteristics were well balanced between the groups, with a median age of 50 years (IQR 43–55; table 1). In the nab-paclitaxel group, 332 patients received 1939 treatment cycles of nab-paclitaxel, with a mean dose of 119·3 mg/m² (SD 14·9) per week. In the docetaxel plus carboplatin group, 337 patients underwent 1980 treatment cycles, with a mean docetaxel dose of 72·6 mg/m² (SD 7·8) every 3 weeks. Carboplatin was administered at a mean AUC of 5·8 mg/mL per min (SD 0·4) every 3 weeks. The cutoff date for this analysis, following the last pathological assessment of complete response, was Aug 18, 2023. Database extraction was conducted on March 7, 2024, and all data were adjusted to align with the clinical cutoff date. The median follow-up time was 26 months (IQR 19–32).

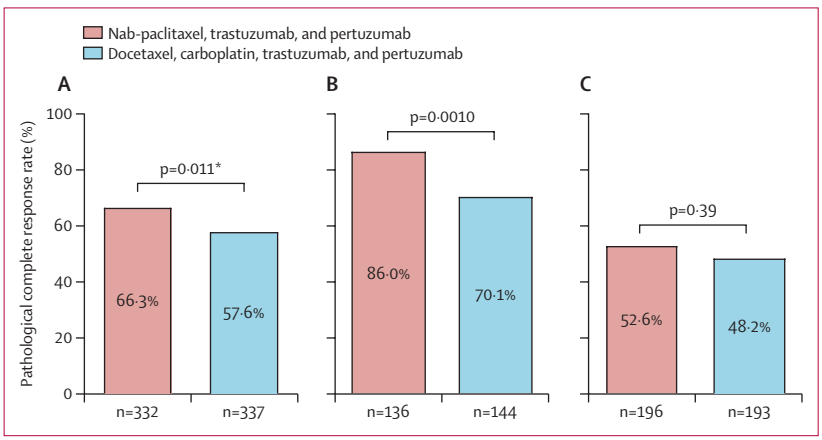

Figure 2: **Pathological complete response rates**
(A) Pathological complete response rate in the modified intention-to-treat population. (B) Pathological complete response rate in hormone receptor-negative patients (oestrogen and progesterone receptor negative). (C) Pathological complete response rate in hormone receptor-positive patients (oestrogen or progesterone receptor positive). Patients with missing or unevaluable pathological complete response status were classified as non-responders. *Cochran-Mantel-Haenszel χ^2 p value. All other p values are results from the χ^2 test.

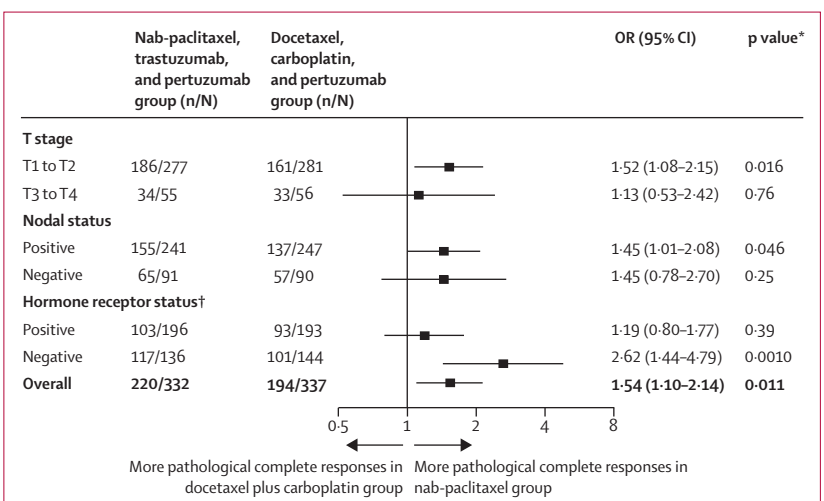

Figure 3: **Subgroup analysis of pathological complete response rates by stratification factors**
*χ^2 test (the p value for overall patients was obtained using the Cochran-Mantel-Haenszel χ^2 test, stratified by tumour stage, nodal status, and hormone receptor status). †Hormone receptor status (oestrogen or progesterone receptor positive is classified as hormone receptor positive; oestrogen and progesterone receptor-negative is classified as hormone receptor-negative).

Overall, 414 (62%) of 669 patients had a pathological complete response. In the nab-paclitaxel group 220 (66·3% [95% CI 61·2–71·4]) of 332 patients had a pathological complete response compared with 194 (57·6% [52·3–62·9]) of 337 patients in the docetaxel plus carboplatin group. The combined OR for pathological complete response was 1·54 (95% CI 1·10–2·14). The lower limit of the 95% CI at 1·10 exceeded 0·80, confirming non-inferiority of the nab-paclitaxel-based regimen. Additionally, the difference in pathological complete response rates between the groups was statistically significant, confirming superiority of the nab-paclitaxel-based regimen (stratified p=0·011; figure 2A). The prespecified exploratory subgroup analyses are shown in figures 2B–C and figure 3. Only hormone receptor status and treatment regimens showed a significant interaction effect on pathological complete response (appendix 2 p 5). Results from post-hoc subgroup analyses are in appendix 2 (p 6). Post-hoc analyses of residual cancer burden and alternate definitions of pathological complete response rate (ypT0 ypN0, ypT0/is ypN0/+, and ypTany ypN0) showed similar results to the main analysis (appendix 2 p 3).

259 (78%) of 332 patients in the nab-paclitaxel group received secondary prevention for treatment-emergent neutropenia and 334 (99%) of 337 patients in the docetaxel plus carboplatin group received pegylated recombinant human G-CSF for primary prophylaxis. Overall, 228 (34%) of 669 patients had at least one grade 3 or 4 adverse event (100 [30%] in the nab-paclitaxel group *vs* 128 [38%] in the docetaxel plus carboplatin group). The most common grade 3–4 adverse events were nausea (22 [7%] in the nab-paclitaxel group *vs* 76 [23%] in the docetaxel plus carboplatin group), diarrhoea (25 [8%] *vs* 55 [16%]), and neuropathy (43 [13%] *vs* eight [2%]; table 2). There were substantially fewer grade 3 or 4 adverse events in the nab-paclitaxel group than the docetaxel plus carboplatin group for anaemia, leukopenia, neutrophilia, thrombocytopenia, nausea, vomiting, and diarrhoea. However, there were higher rates of grade 3 or 4 adverse events in the nab-paclitaxel group than in the docetaxel plus carboplatin

group for neuropathy, increased alanine aminotransferase, and increased aspartate aminotransferase (table 2). A decline in a left ventricular ejection fraction of 10 or more percentage points from baseline to less than 50% was observed in one (<1%) patient in the nab-paclitaxel group and in two (1%) patients in the docetaxel plus carboplatin group. Symptomatic left ventricular systolic dysfunction did not occur in either group. Serious drug-related adverse events were observed in three (1%) patients receiving nab-paclitaxel (severe neuropathy) and five (2%) patients receiving docetaxel plus carboplatin (two severe diarrhoea and three severe thrombocytopenia). No treatment-related deaths were reported.

Dose reductions were required in 57 (17%) of 332 patients in the nab-paclitaxel group, and 86 (26%) of 337 patients in the docetaxel plus carboplatin group. Specifically, 16 (5%) patients in the docetaxel plus carboplatin group required dose reductions of docetaxel, 65 patients (19%) required dose reductions of carboplatin, and five patients (2%) required dose reductions of both. The most common reasons for dose reductions in the nab-paclitaxel group were neuropathy (36 [11%] of 332), whereas in the docetaxel plus carboplatin group, the primary reasons were blood and lymphatic system disorders for docetaxel (12 [4%] of 337) and gastrointestinal disorders for carboplatin (49 [15%] of 337). Discontinuation was observed in 31 (9%) patients in the nab-paclitaxel group (due to 19 non-progression-related adverse events, five withdrawals of consent, two cases of progressive disease, and five other reasons) and in 23 (7%) patients in the docetaxel plus carboplatin group (due to 11 non-progression-related adverse events [seven of carboplatin and four of both docetaxel and carboplatin], two withdrawals of consent, four cases of progressive disease, and six other reasons; figure 1).

	Nab-paclitaxel, trastuzumab, and pertuzumab group (n=332)			Docetaxel, carboplatin, trastuzumab, and pertuzumab group (n=337)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Haematological adverse events						
Anaemia	298 (90%)	2 (1%)	0	289 (86%)	13 (4%)	0
Leukopenia	114 (34%)	1 (<1%)	0	120 (36%)	17 (5%)	0
Neutrophilia	236 (71%)	9 (3%)	0	206 (61%)	20 (6%)	0
Febrile neutropenia	NA	5 (2%)	0	NA	13 (4%)	0
Thrombocytopenia	116 (35%)	5 (2%)	0	143 (42%)	15 (4%)	2 (1%)
Non-haematological adverse events						
Nausea	229 (69%)	22 (7%)	0	233 (69%)	76 (23%)	0
Vomiting	81 (24%)	4 (1%)	0	174 (52%)	27 (8%)	0
Diarrhoea	226 (68%)	25 (8%)	0	261 (77%)	55 (16%)	0
Constipation	69 (21%)	0	0	90 (27%)	0	0
Abdominal pain	166 (50%)	3 (1%)	0	192 (57%)	4 (1%)	0
Myalgia	210 (63%)	1 (<1%)	0	223 (66%)	4 (1%)	0
Arthralgia	158 (48%)	4 (1%)	0	164 (49%)	4 (1%)	0
Neuropathy	266 (80%)	43 (13%)	0	231 (69%)	8 (2%)	0
Dysgeusia	323 (97%)	0	0	329 (98%)	0	0
Mucositis or stomatitis	107 (32%)	3 (1%)	0	113 (34%)	4 (1%)	0
Laboratory-assessed items						
Increased alanine aminotransferase	203 (61%)	13 (4%)	0	136 (40%)	3 (1%)	0
Increased aspartate aminotransferase	164 (49%)	13 (4%)	0	128 (38%)	0	0
Increased alkaline phosphatase	175 (53%)	0	0	125 (37%)	0	0
Increased creatinine	10 (3%)	0	0	38 (11%)	0	0
Hypokalaemia	21 (6%)	1 (<1%)	0	80 (24%)	0	0
Hyponatraemia	31 (9%)	1 (<1%)	0	32 (9%)	0	0
Hypocalcaemia	20 (6%)	1 (<1%)	1 (<1%)	19 (6%)	0	0

Data are all grade 1 or grade 2 adverse events that occurred in ≥10% of patients in either treatment group and all grade 3 and grade 4 adverse events. No deaths occurred in either group. Patients might have had more than one adverse event. NA=not applicable.

Table 2: **Adverse events**

Discussion

In this randomised, phase 3 clinical trial investigating neoadjuvant treatment of Asian women with HER2-positive early breast cancer, the combination of nab-paclitaxel, trastuzumab, and pertuzumab significantly improved the pathological complete response rate compared with the standard regimen of docetaxel, carboplatin, trastuzumab, and pertuzumab. This improvement was particularly pronounced in the hormone receptor-negative subgroup but there was no significant improvement in the hormone receptor-positive subgroup. The nab-paclitaxel regimen resulted in fewer grade 3 or worse adverse events than the docetaxel plus carboplatin regimen, despite higher rates of neuropathy and elevated liver enzymes in the nab-paclitaxel group. Although the correlation between pathological complete response and long-term outcomes is well established,[19,20] extended follow-up is needed to evaluate the potential survival benefits.

In this trial, the studied regimen omitted carboplatin and replaced solvent-based docetaxel with albumin-bound paclitaxel. The BCIRG007[21] and APT[22] studies showed success in omitting carboplatin for advanced and some early-stage breast cancers. The GeparSixto phase 2 trial[23] confirmed that adding carboplatin to a regimen of anthracycline, taxane, trastuzumab, and lapatinib did not improve the pathological complete response rate in patients with HER2-positive cancers. The current trial supported findings that reducing chemotherapy to a single agent in combination with dual targeted therapy did not compromise the neoadjuvant treatment pathological complete response rate in patients with HER2-positive breast cancer. Ongoing studies such as CompassHER2-pCR (NCT04266249) are assessing the effectiveness of paclitaxel, trastuzumab, and pertuzumab in eliminating additional chemotherapy after surgery in patients with HER2-positive breast cancer with no residual cancer after preoperative treatment. Although both CompassHER2-pCR and HELEN-006 explore the efficacy of single-agent taxane chemotherapy with

trastuzumab and pertuzumab for neoadjuvant treatment, they differ substantially in their primary endpoints and study designs. Results from CompassHER2-pCR might provide evidence for the use of single-agent paclitaxel in combination with dual-targeted therapy.

The GeparSepto study[12,13] showed that weekly nab-paclitaxel significantly enhances the rate of pathological complete response in patients receiving neoadjuvant breast cancer treatment compared with weekly paclitaxel. In the analysis of the HER2-positive subgroup, although there was no statistically significant difference in the pathological complete response rates (ypT0N0) between the two groups, a numerical increase of 8% was observed. In the survival analysis in GeparSepto, although there was also no statistical difference in invasive disease-free survival, the comparative HR was 0·63 (95% CI 0·35–1·14). It is important to note that the subgroup analysis in the GeparSepto study was exploratory, and the small sample size was insufficient to provide adequate statistical power for either the pathological complete response or invasive disease-free survival comparisons. A sufficient sample size might also be why our study could yield positive results. In this trial, the pathological complete response rate after six cycles of nab-paclitaxel combined with trastuzumab and pertuzumab was 66·3%, which is similar to the 66·2% reported in the GeparSepto study.[24] However, the chemotherapy regimen in this trial involved only a single chemotherapy drug for six cycles, in contrast to the multiple agents used in GeparSepto for eight cycles. This comparison indirectly suggests that adding an anthracycline to dual-targeted therapy with nab-paclitaxel might not further enhance pathological complete response rates in patients HER2-positive breast cancer. This theory possibility aligns with the TRAIN-2 study,[25] which found similar pathological complete response rates with or without an anthracycline.

In the HER2-positive and hormone receptor-negative subgroup specifically, nab-paclitaxel with trastuzumab and pertuzumab significantly increased the pathological complete response rate compared with the standard regimen. The 86·0% pathological complete response rate observed with six cycles of nab-paclitaxel in this subgroup in this phase 3 HELEN-006 study is close to the 91% reported in the WSG ADAPT HER2+/HR– phase 2 study.[7] Differing from the WSG ADAPT HER2+/HR– phase 2 study, the HELEN-006 study had a higher proportion of patients with lymph node-positive disease (73% *vs* 38% in the WSG ADAPT HER2+/HR– study). Moreover, compared to the sample size of 42 patients in the WSG ADAPT HER2+/HR– study, our study included a larger subgroup sample size of 136 patients, which provides greater statistical power. However, confirmatory conclusions will require rigorously designed prospective studies for validation.

For patients with HER2-positive and hormone receptor-positive breast cancers, the increase in pathological complete response rate with nab-paclitaxel combined with trastuzumab and pertuzumab was not significant, although there was a slight numerical increase. Additionally, the lower rate of adverse events associated with nab-paclitaxel than with docetaxel and carboplatin might be advantageous for these patients. Regardless, in this subgroup, the 52·6% pathological complete response rate from six cycles of nab-paclitaxel in HELEN-006 is similar to the 56% from four cycles of paclitaxel in the WSG-TP-II trial,[26] despite a higher proportion of lymph node-positive patients in the HELEN-006 trial (73% *vs* 24% in the WSG-TP-II trial). Further exploration is needed to establish the optimal chemotherapy cycles and taxane types for this subgroup of patients.

Because HER2-positive and hormone receptor-positive subgroups are sensitive to endocrine and targeted therapies, studies have explored combining targeted therapy with endocrine therapy while omitting chemotherapy.[6,8] However, in the WSG-TP-II study,[26] 12 weeks of endocrine therapy combined with trastuzumab and pertuzumab had a significantly lower pathological complete response rate than 12 weeks of paclitaxel combined with trastuzumab and pertuzumab (24% *vs* 56%; p<0·001). Additionally, in the WSG-ADAPT-TP study,[27] adding endocrine therapy to trastuzumab emtansine did not improve the pathological complete response rate of neoadjuvant therapy (41% *vs* 42%). Therefore, chemotherapy remains important in maximising the pathological complete response rate in the neoadjuvant treatment of this subgroup. Single-agent taxane chemotherapy combined with dual-targeted therapy might represent an ideal treatment regimen for the neoadjuvant setting in HER2-positive and hormone receptor-positive subgroups.

In our study, the nab-paclitaxel group had substantially fewer grade 3–4 adverse events than the standard treatment group, primarily due to reduced haematological and gastrointestinal reactions. However, the incidence of neurotoxicity was higher in the nab-paclitaxel group, with the majority of these adverse events being grade 1–2. Only 13% of patients in the nab-paclitaxel group had grade 3–4 neurotoxicity, which is consistent with the 11% reported in the GeparSepto study,[12] in which the median time for recovery from grade 3–4 to grade 1 neurotoxicity was 17 weeks. The follow-up period in this study is still short, and we will continue to monitor the time to recovery of neurotoxicity.

This study has several limitations. First, we selected pathological complete response as our primary outcome measure. Patients who have a pathological complete response generally have better event-free and overall survival.[19,20] However, it remains unclear how large the difference in pathological complete response rate between two treatment groups must be to translate into a clinically meaningful survival benefit. The use of pathological complete response as a surrogate for long-term outcomes remains highly controversial.[28–30]

We are also tracking event-free survival and invasive disease-free survival, with findings to be reported in due course. However, it should be noted that the sample size calculation for this study was based on the primary endpoint of pathological complete response rate, and the comparison of survival outcomes between the two groups might not have sufficient statistical power. Additionally, the trial's geographical limitation to China might affect the generalisability of the findings.

In conclusion, the HELEN-006 study showed a pathological compete response rate in the overall population similar to that of the GeparSepto study, despite using a different chemotherapy regimen with only a single agent. The pathological complete response rate in the hormone receptor-negative subgroup aligned with the rate in the WSG ADAPT HER2+/HR– trial, and the rate in the hormone receptor-positive subgroup was similar to that reported in the WSG-TP-II trial. Unlike these trials, which used varying numbers of cycles and different taxanes, HELEN-006 uniquely included a standardised chemotherapy regimen in the control group.

To our knowledge, the HELEN-006 study is the first prospective, randomised, phase 3 trial comparing a weekly nab-paclitaxel regimen with dual HER2 blockade to the standard docetaxel plus carboplatin regimen with dual HER2 blockade in patients with HER2-positive early stage breast cancer. In addition to having fewer adverse events, the patients receiving the 18-week nab-paclitaxel regimen had higher pathological complete response rates than the control group, showing that this treatment regimen can reduce toxicity without compromising efficacy. Extended follow-up is necessary and ongoing to evaluate the long-term benefits.

Contributors

X-CC, D-CJ, J-HQ, and C-ZW are co-first authors and contributed equally to the work. Z-ZL conceived and designed the study. X-CC, D-CJ, J-HQ, C-ZW, X-FS, Z-DL, L-FL, C-JZ, MY, YW, BC, Y-QF, MD, and M-DM recruited patients. X-CC, D-CJ, J-HQ, C-ZW, and Z-DL collected data. X-CC and Z-ZL accessed and verified the data in the study. All authors contributed to the analysis and interpretation of data. All authors contributed to the preparation and critical review of the manuscript. Y-WH and Z-ZL contributed to the study supervision. X-CC, D-CJ, and J-HQ contributed to the administrative support. All authors had access to all the data reported in this study and approved the final version of manuscript for submission. The report was reviewed by all authors. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Individual participant data (including data dictionaries) that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices), are available immediately and ending 3 years after article publication. Oncologists can gain access to the data from the corresponding author upon written request. After 3 years, data will be not available. Study protocol, statistical analysis plan, and informed consent form are not available.

Acknowledgments

The study was supported by the Training Program for Young and Middle-aged Health and Technology Innovation Leaders in Henan Province (YXKC2022005, LJRC2023003), the National Natural Science Foundation of China (number 82372712), and the Science and Technology Research Projects of Henan province (number 232102311125). We thank all the patients who participated in this trial and their families, as well as the investigators and staff at each study site. We thank Li Kong (President of Academy of Clinical Research and Study) for coordinating this research work and communication, Meishuo Ouyang (Department of Surgery, Duke University School of Medicine, Duke University, Durham, NC, USA), and Yinting Liu (Department of Biostatistics, School of Global Public Health, New York University, New York NY, USA) for their input in language polishing of the manuscript.

References

1 Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989; **244:** 707–12.

2 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70:** 7–30.

3 Bradley R, Braybrooke J, Gray R, et al. Trastuzumab for early-stage, HER2-positive breast cancer: a meta-analysis of 13 864 women in seven randomised trials. *Lancet Oncol* 2021; **22:** 1139–50.

4 von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med* 2017; **377:** 122–31.

5 Choong GM, Cullen GD, O'Sullivan CC. Evolving standards of care and new challenges in the management of HER2-positive breast cancer. *CA Cancer J Clin* 2020; **70:** 355–74.

6 Pérez-García JM, Gebhart G, Ruiz Borrego M, et al. Chemotherapy de-escalation using an ^{18}F-FDG-PET-based pathological response-adapted strategy in patients with HER2-positive early breast cancer (PHERGain): a multicentre, randomised, open-label, non-comparative, phase 2 trial. *Lancet Oncol* 2021; **22:** 858–71.

7 Nitz UA, Gluz O, Christgen M, et al. De-escalation strategies in HER2-positive early breast cancer (EBC): final analysis of the WSG-ADAPT HER2+/HR– phase II trial: efficacy, safety, and predictive markers for 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab ± weekly paclitaxel. *Ann Oncol* 2017; **28:** 2768–72.

8 Hurvitz SA, Martin M, Symmans WF, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol* 2018; **19:** 115–26.

9 Llombart-Cussac A, Cortés J, Paré L, et al. HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial. *Lancet Oncol* 2017; **18:** 545–54.

10 Guarneri V, Dieci MV, Bisagni G, et al. De-escalated therapy for HR+/HER2+ breast cancer patients with Ki67 response after 2-week letrozole: results of the PerELISA neoadjuvant study. *Ann Oncol* 2019; **30:** 921–26.

11 Gradishar WJ. Albumin-bound paclitaxel: a next-generation taxane. *Expert Opin Pharmacother* 2006; **7:** 1041–53.

12 Untch M, Jackisch C, Schneeweiss A, et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): a randomised, phase 3 trial. *Lancet Oncol* 2016; **17:** 345–56.

13 Untch M, Jackisch C, Schneeweiss A, et al. NAB-paclitaxel improves disease-free survival in early breast cancer: GBG 69-GeparSepto. *J Clin Oncol* 2019; **37:** 2226–34.

14 Compton CC, Byrd DR, Garcia-Aguilar J, Kurtzman SH, Olawaiye A, Washington MK, eds. AJCC cancer staging atlas. 2nd edn. New York, NY: Springer-Verlag, 2012.

15 Nielsen TO, Leung SCY, Rimm DL, et al. Assessment of Ki67 in breast cancer: updated recommendations from the International Ki67 in Breast Cancer Working Group. *J Natl Cancer Inst* 2020; **113:** 808–19.

16 National Cancer Institute. Common terminology criteria for adverse events v.4.0 (CTCAE). http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (accessed Aug 9, 2024).

17 The European Agency for the Evaluation of Medicinal Products. Points to consider on switching between superiority and non-inferiority. https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-switching-between-superiority-and-non-inferiority_en.pdf (accessed July 20, 2024).

18 US Department of Health and Human Services, Food and Drug Administration. Non-inferiority clinical trials to establish effectiveness—guidance for industry. 2016. https://www.fda.gov/media/78504/download (accessed Aug 1, 2024).

19 van Mackelenbergh MT, Loibl S, Untch M, et al. Pathologic complete response and individual patient prognosis after neoadjuvant chemotherapy plus anti-human epidermal growth factor receptor 2 therapy of human epidermal growth factor receptor 2-positive early breast cancer. *J Clin Oncol* 2023; **41:** 2998–3008.

20 Squifflet P, Saad ED, Loibl S, et al. Re-evaluation of pathologic complete response as a surrogate for event-free and overall survival in human epidermal growth factor receptor 2-positive, early breast cancer treated with neoadjuvant therapy including anti-human epidermal growth factor receptor 2 therapy. *J Clin Oncol* 2023; **41:** 2988–97.

21 Valero V, Forbes J, Pegram MD, et al. Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 study): two highly active therapeutic regimens. *J Clin Oncol* 2011; **29:** 149–56.

22 Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med* 2015; **372:** 134–41.

23 von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol* 2014; **15:** 747–56.

24 Loibl S, Jackisch C, Schneeweiss A, et al. Dual HER2-blockade with pertuzumab and trastuzumab in HER2-positive early breast cancer: a subanalysis of data from the randomized phase III GeparSepto trial. *Ann Oncol* 2017; **28:** 497–504.

25 van Ramshorst MS, van der Voort A, van Werkhoven ED, et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2018; **19:** 1630–40.

26 Gluz O, Nitz UA, Christgen M, et al. Efficacy of endocrine therapy plus trastuzumab and pertuzumab *vs* de-escalated chemotherapy in patients with hormone receptor-positive/ERBB2-positive early breast cancer: the neoadjuvant WSG-TP-II randomised clinical trial. *JAMA Oncol* 2023; **9:** 946–54.

27 Harbeck N, Gluz O, Christgen M, et al. De-escalation strategies in human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (BC): final analysis of the west German nab-paclitaxel group adjuvant dynamic marker-adjusted personalized therapy trial optimizing risk assessment and therapy response prediction in early BC HER2- and hormone receptor-positive phase ii randomised trial-efficacy, safety, and predictive markers for 12 weeks of neoadjuvant trastuzumab emtansine with or without endocrine therapy (ET) versus trastuzumab plus ET. *J Clin Oncol* 2017; **35:** 3046–54.

28 Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet* 2010; **375:** 377–84.

29 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:** 1137–46.

30 Huang L, Pang D, Yang H, et al. Neoadjuvant-adjuvant pertuzumab in HER2-positive early breast cancer: final analysis of the randomized phase III PEONY trial. *Nat Commun* 2024; **15:** 2153.