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Study Protocol

Omission of Breast Surgery in Predicted Pathologic Complete Response after Neoadjuvant Systemic Therapy: A Multicenter, Single-Arm, Non-inferiority Trial

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ABSTRACT

Purpose: Advances in chemotherapeutic and targeted agents have increased pathologic complete response (pCR) rates after neoadjuvant systemic therapy (NST). Vacuum-assisted biopsy (VAB) has been suggested to accurately evaluate pCR. This study aims to confirm the non-inferiority of the 5-year disease-free survival of patients who omitted breast surgery when

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Trial Registration
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predicted to have a pCR based on breast magnetic resonance imaging (MRI) and VAB after NST, compared with patients with a pCR who had undergone breast surgery in previous studies.
Methods: The Omission of breast surgery for PredicTed pCR patients wIth MRI and vacuum-assisted bIopsy in breaST cancer after neoadjuvant systemic therapy (OPTIMIST) trial is a prospective, multicenter, single-arm, non-inferiority study enrolling in 17 tertiary care hospitals in the Republic of Korea. Eligible patients must have a clip marker placed in the tumor and meet the MRI criteria suggesting complete clinical response (post-NST MRI size ≤ 1 cm and lesion-to-background signal enhancement ratio ≤ 1.6) after NST. Patients will undergo VAB, and breast surgery will be omitted for those with no residual tumor. Axillary surgery can also be omitted if the patient was clinically node-negative before and after NST and met the stringent criteria of MRI size ≤ 0.5 cm. Survival and efficacy outcomes are evaluated over five years.
Discussion: This study seeks to establish evidence for the safe omission of breast surgery in exceptional responders to NST while minimizing patient burden. The trial will address concerns about potential undertreatment due to false-negative results and recurrence as well as improved patient-reported quality of life issues from the omission of surgery. Successful completion of this trial may reshape clinical practice for certain breast cancer subtypes and lead to a safe and less invasive approach for selected patients.

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Keywords: Biopsy; Breast Neoplasms; Clinical Trial; Multicenter Study; Neoadjuvant Therapy

INTRODUCTION

Neoadjuvant systemic therapy (NST) has been increasingly adopted as the preferred treatment for hormone receptor (HR)-negative and human epidermal growth factor receptor 2 (HER2)-positive breast cancers. It has several advantages over upfront surgery, including early observation of systemic therapy response and tumor size reduction before surgery [1-3]. Response to NST and the rate of pathologic complete response (pCR) differ by the molecular subtype of breast cancer [4], and achieving pCR is known to be significantly associated with favorable oncologic outcomes [5,6]. While HR-positive breast cancer shows a poor response to chemotherapy, triple-negative breast cancer (TNBC) and HER2-positive breast cancer show a favorable response to NST and a higher pCR rate. Accordingly, major guidelines recommend NST for patients with stage II or higher TNBC and HER2-positive breast cancers [7]. In addition, estrogen receptor (ER)-low-positive (< 10%) tumors are treated similarly to ER-negative tumors, as their treatment response after NST is closer to that of TNBC than that of HR-positive breast cancer [8]. Moreover, with advances in systemic therapy regimens, including cytotoxic chemotherapy, HER2-targeted therapy, and immunotherapy, the rate of achieving pCR after NST has reached up to 40%–50%, 60%–70%, and 30%–40% in TNBC, HER2-positive, and ER-low-positive breast cancer, respectively [6,8,9].

The question arises as to whether surgery is necessary even after achieving pCR. Surgery after NST plays a crucial role in the excision of residual tumors and their surrounding tissues in non-pCR cases. In contrast, for patients with pCR, surgery may only serve to pathologically confirm the absence of residual disease. Between the 1970s and 1990s, several studies investigated the survival outcomes of omitting surgery and performing radiotherapy alone

Conflict of Interest

Jiwon Koh reported receiving consultation fees from DCGen. Co., Ltd., outside the submitted work. Hee-Chul Shin, Wonshik Han, and Han-Byoel Lee reported being member of the board of directors of and holding stock and ownership interests at DCGen, Co, Ltd., outside the submitted work. Han-Byoel Lee reported receiving grants in the form of Mammotome® Elite needles from Devicor Medical Products, Inc. for this work. The grant source had no part in the design and preparation of the protocol. No other disclosures were reported.

Data Availability

In accordance with the ICMJE data-sharing policy, the authors agree to make data available upon request.

Author Contributions

Conceptualization: Kim MK, Lee HB; Funding acquisition: Lee HB; Investigation: Jung JJ, Cheun JH, Kim SY, Koh J, Ryu JM, Yoo TK, Shin HC, Ahn SG, Park S, Lim W, Nam SE, Park MH, Kim KS, Kang T, Lee J, Youn HJ, Kim YS, Yoon CI, Kim HK, Moon HG, Han W, Cho N, Kim MK, Lee HB; Methodology: Jung JJ, Cheun JH, Kim SY, Koh J, Cho N, Kim HK, Han W, Kim MK, Lee HB; Supervision: Moon HG, Han WS; Writing - original draft: Jung JJ, Cheun JH, Kim MK, Lee HB; Writing - review & editing: Jung JJ, Cheun JH, Kim SY, Koh J, Ryu JM, Yoo TK, Shin HC, Ahn SG, Park S, Lim W, Nam SE, Park MH, Kim KS, Kang T, Lee J, Youn HJ, Kim YS, Yoon CI, Kim HK, Moon HG, Han W, Cho N, Kim MK, Lee HB.

when a complete clinical response (cCR) was expected after NST, but these resulted in higher locoregional recurrence rates [10]. However, these studies were conducted nearly three to five decades ago, and their methodological features do not reflect recent advances in pathologic and radiologic diagnosis, minimally invasive biopsy techniques, and the increase in pCR rates. Among these early studies, Ring et al. [11] reported that omitting surgery had a local recurrence rate of only 8% when cCR was predicted using ultrasound, which was comparable to that in patients who underwent surgery. This suggests the possibility of omitting surgery when pCR can be accurately predicted using other modalities.

Several early feasibility studies have evaluated the usefulness of minimally invasive biopsies in predicting pCR [12-14]. The studies consisted of a biopsy of the primary tumor bed after NST and a subsequent wide excision of the same area, followed by a comparison of whether there was a residual tumor in both specimens. Heil et al. [12] reported the results of 9 to 11 G vacuum-assisted biopsy (VAB) or 14 G core needle biopsy (CNB) in 164 patients with cCR, showing an unacceptable 49.3% false-negative rate (FNR). However, they showed an improved negative predictive value (NPV) in patients with a clip marker placed in the primary tumor. In a subsequent study, the same group performed 9 G VAB in 50 patients with partial or cCR and showed an improved FNR of 25.9%. In their study, they achieved an FNR of 4.8% for specimens confirmed to have a histopathological evaluation of representativeness [13]. A feasibility trial conducted by Kuerer et al. [14] reported an FNR of 5% using image-guided fine-needle aspiration and VAB in patients with radiological complete response on post-NST mammography and sonography.

Although surgery is still the standard treatment for patients expected to achieve pCR, recent studies suggest that surgery can be omitted if pCR can be more accurately predicted and an alternative method other than surgery is available to confirm pCR. We previously conducted a study on a method for accurately predicting pCR and demonstrated that features of contrast-enhanced magnetic resonance imaging (MRI) after NST are helpful. Analyzing 216 patients, the criterion of lesion-to-background signal enhancement ratio (L-to-B SER) ≤ 1.6 and/or tumor size ≤ 0.2 cm on MRI after NST showed a specificity of 90.4% in identifying pCR [15]. In addition, core needle biopsy or VAB for patients satisfying the criteria of a L-to-B SER ≤ 1.6 or tumor size ≤ 0.5 cm on MRI showed an accuracy of 90.0% for correctly predicting the pCR [16]. Especially, NPV and FNR were 100.0% and 0%, respectively, when at least five biopsy cores were obtained based on tumor size ≤ 0.5 cm and a L-to-B SER ≤ 1.6 on MRI. Lastly, a pooled analysis of data from MD Anderson Cancer Center [14], the Royal Marsden, and Seoul National University Hospital [16] showed that pCR could be predicted with an NPV and FNR of 97.4% and 3.2%, respectively, when VAB collected six or more cores for lesions of 2 cm or less remaining on imaging [17].

The findings of the aforementioned studies indicate that pCR can be predicted with high accuracy using VAB after NST in patients who meet specific MRI criteria. These results were utilized to design a multicenter clinical trial to establish evidence for omitting surgery in patients with TNBC, HER-2 positive, or ER-low-positive breast cancer who are expected to achieve a pCR on MRI and confirmed to have no residual tumor on VAB.

METHODS

Study goal

This study is designed to confirm the non-inferiority of the 5-year disease-free survival (DFS) of patients who are omitted breast surgery when predicted to have a pCR based on breast MRI and VAB after NST, compared with patients with a pCR who had undergone breast surgery in previous studies.

Study design and participants

The Omission of breast surgery for PredicTed pCR patients with MRI and vacuum-assisted bIopsy in breaST cancer after neoadjuvant systemic therapy (OPTIMIST) trial is a prospective, multicenter, single-arm, non-inferiority clinical study. Seventeen tertiary care hospitals in the Republic of Korea are participating in this study (**Supplementary Table 1**). Women aged 19–75 years who had pathologically confirmed invasive ductal carcinoma and completed the NST using MRI criteria suggesting cCR are eligible for inclusion. The MRI criteria for cCR were defined as both an enhanced tumor size of ≤ 1 cm with an L-to-B SER of ≤ 1.6 [16]. Placing a clip marker in the tumor before or during NST is a prerequisite for enrollment in this trial. The eligible breast cancer subtypes are HER2-positive (regardless of HR status), triple-negative (ER-negative, progesterone receptor-negative, and HER2-negative), or ER-low-positive (defined as ER expression < 10% by immunohistochemistry) breast cancer. HR negativity is defined as < 1% of cells positive for ER and progesterone receptor, and HER2 positivity is defined as 3+ or 2+ on immunohistochemistry and amplified by fluorescence or silver in situ hybridization, according to American Society of Clinical Oncology/College of American Pathologists guidelines [7]. The extent of the disease is limited to clinical T1-2 (defined as the largest tumor diameter ≤ 5 cm on breast ultrasound or physical examination), clinical N0-2, and no evidence of distant metastasis.

After the completion of or before the last cycle of the NST regimen, all patients undergo breast MRI and mammography. Patients who meet the MRI criteria for cCR will be considered for enrollment. However, patients are not eligible for inclusion if they have residual malignant calcification > 2 cm on mammogram after NST, multifocal cancer ≥ 2 lesions, bilateral breast cancer, history of contralateral breast cancer or any malignancy within five years, inflammatory breast cancer, or if they are pregnant. Patients with contraindications for radiotherapy, those who had an allergic history to contrast media for MRI, *BRCA* 1/2 pathogenic or likely pathogenic mutation carriers, or those willing to undergo mastectomy will also be excluded.

Ethics and dissemination

The Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. H2202-065-1299; first approved on July 25, 2022) approved the trial protocol (version 6.6; approved on December 26, 2022), and all patients will provide written informed consent to participate. The IRB of all participating sites approved the trial protocol. This trial has been registered at ClinicalTrials.gov (NCT05505357) and cris.nih.go.kr (KCT0007638). Modifications to the protocol beyond the current version will be made with the agreement of all the investigators. Following IRB approval, changes will be updated in the trial registry.

Procedures

When a patient meets the MRI criteria suggestive of a cCR, VAB targeting the primary lesion is performed under ultrasound or stereotactic guidance. A minimum of six cores, including

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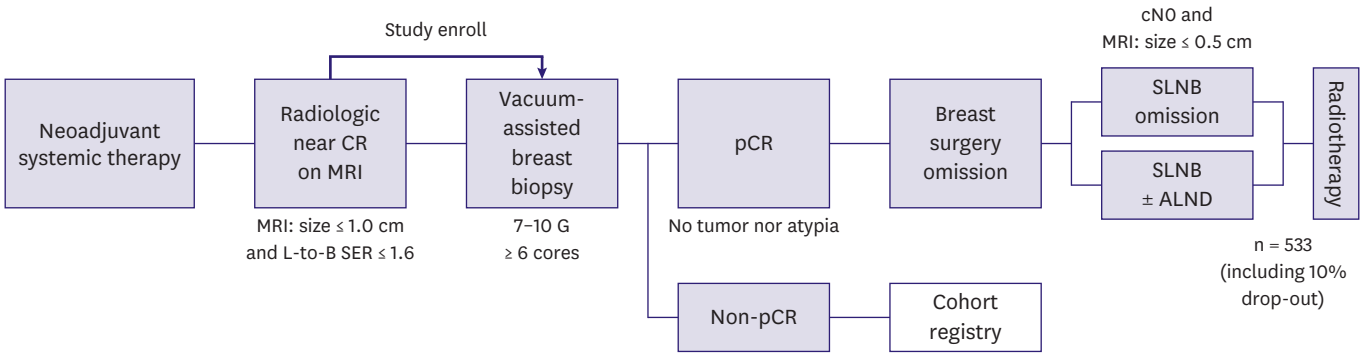

Figure 1. Study design.
CR = complete response; MRI = magnetic resonance imaging; L-to-B SER = lesion-to-background signal enhancement ratio; pCR = pathologic complete response; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection

post-NST changes around the clip, are obtained using a 7–10 G needle. Biopsy specimens are examined by a pathologist to assess the residual tumor and tumor bed (**Figure 1**).

The VAB sample is considered representative and valid when the clip is retrieved or pathologic evidence of the tumor bed, including fibrosis/scarring, foamy macrophages, hemosiderin-laden macrophages, hemosiderin deposition, stromal elastosis, myxoid change, or stromal mucin, is observed [18]. When no tumor or atypical cells are confirmed in the valid VAB specimen, the patient is omitted from breast surgery. For patients with no suspicious lymph node metastasis before and after NST and tumor size ≤ 0.5 cm with L-to-B SER ≤ 1.6 on MRI after NST, sentinel lymph node biopsy (SLNB) could also be omitted according to the discretion of the surgeon. For patients with cN1-2 disease or post-NST tumor size > 0.5 cm on MRI, SLNB with or without axillary lymph node dissection is performed. Patients with residual tumors or atypical cells proceed with standard surgery as recommended by the surgeons and are registered in a prospective registry for survival comparison with patients who have undergone breast surgery omission. After the VAB procedure, all patients are asked to grade their perceived pain using a visual analog scale (VAS) on the first and third days.

Surveillance

All patients receive adjuvant radiation therapy for the breast within eight weeks from the latter date of VAB or axillary surgery. Adjuvant anti-hormonal and targeted therapies are administered to the indicated patients. Patients are followed-up every six months until the second year and every year thereafter for five years. Surveillance breast MRI is required at 1- and 2-year follow-up visits, and mammography annually for five years. Additional systemic examinations and workups will be performed according to the practices and circumstances of each institution and investigator. If any evidence of recurrence is found near the VAB site in the breast or within the breast during follow-up, a core needle biopsy, VAB, or excisional biopsy should be performed to evaluate the recurrence. Quality of life (QoL) questionnaires (EORTC QLQ-30 and EORTC QLQ-BR23) will be collected at enrollment and at the 1-year follow-up visit. The study design is shown in **Figure 1**, and the schedule of enrollment, interventions, and assessments are shown in **Figure 2**, in the format recommended by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The SPIRIT checklist is presented in **Supplementary Table 2**.

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	Study period									
	Enrollment & Allocation			Post-allocation						Closeout
Timepoint	**−4 weeks**	**−3 weeks**	**0**	**8 weeks**	**6 months**	**1-year**	**1.5-year**	**2-year**	**3,4-year**	**5-year**
Enrollment										
Eligibility screen	x	x								
Informed consent	x									
Interventions										
Vacuum-assisted biopsy		x								
Axillary surgery			x							
Radiotherapy				x						
Assessments										
Demographics	x									
Medical history	x									
Physical examination	x				x	x	x	x	x	x
Electrocardiogram	x*									
Laboratory tests	x*				x	x	x	x	x	x
Breast MRI	x					x		x		
Mammography	x					x		x	x	x
Breast ultrasonography	x									
Additional questionnaires										
EORTC QLQ-30	x					x				
EORTC QLQ-BR23	x					x				
Visual analog scale		x								
Medical cost										x

*Test results conducted prior to the screening visit can be used.

Figure 2. Timepoints for enrollment, interventions, and assessments.
MRI = magnetic resonance imaging.

Sample size calculation

We designed the OPTIMIST trial to determine whether the 5-year DFS of patients who do not undergo breast surgery after pCR is confirmed with VAB is not inferior to that of patients who received standard breast surgery and were confirmed to have pCR. In the CTNeoBC pooled analysis, the 5-year event-free survival rate was approximately 85% for both TNBC and HER2-positive breast cancer [5]. In a meta-analysis of the impact of pCR after NST on breast cancer recurrence and survival conducted by Spring et al. [6], the 5-year event-free survival of patients with pCR was 90% for TNBC and 86% for HER2-positive breast cancer. Considering the improvement in therapeutic regimens and the conservative approach, we assumed the expected 5-year DFS of the control group to be 88%.

The one-sided test with a non-inferiority margin of 4% and statistical power of 80% at a significance level of 0.05 resulted in a sample size of 384 patients to be omitted from breast

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surgery. Assuming that the probability of residual lesions on VAB was 20% [15,16], the total number of participants is 480. Considering a dropout rate of 10%, 533 participants will be enrolled.

Safety monitoring

The study will be suspended after enrolling 50% of the target patients, and interim futility analyses will be conducted once the participants have undergone a median follow-up period of one year. The Data Safety Monitoring Board (DSMB) will determine the continuation of the trial by confirming the 1-year DFS. According to previous studies, the DFS of patients who omitted surgery should not be < 84% [5,6,19,20]. Assuming an exponential distribution for DFS, the expected 1-year DFS becomes 97.0%. Therefore, the DSMB will consider termination if the result shows a 1-year DFS of 97% or less. All adverse events will be monitored and reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

Study outcomes

The primary endpoint is the 5-year DFS, and the secondary endpoints are the 5-year ipsilateral breast tumor recurrence-free survival, 5-year overall survival, 5-year invasive DFS, rate of residual axillary lymph node metastasis, QoL scores (EORTC QLQ-30 and EORTC QLQ-BR23), symptoms (VAS score), and medical costs.

Data management and monitoring

The principal investigator has full responsibility for monitoring the entire investigation. Sub-investigators at each institution will collect medical data, anonymize private information, and store it in an electronic case report form. To ensure data accuracy, the clinical research organization will routinely monitor the collected data, and the DSMB will serve as an independent committee to ensure data integrity and patient safety.

Statistical analysis

The primary endpoint (5-year DFS) will be analyzed in the per-protocol population who were omitted from breast surgery, and the secondary endpoints will be analyzed in the intention-to-treat populations. The Kaplan–Meier analysis model will be used to estimate survival curves, and the log-rank test will be used to test for non-inferiority. Nominal variables will be assessed using a χ^2 or Fisher's exact test, and continuous variables will be analyzed using the Student's *t*-test or Mann–Whitney *U* test. For every statistical analysis, a *p*-value of < 0.05 will be considered statistically significant. The Medical Research Collaborating Center of Seoul National University Hospital will perform the statistical analyses.

DISCUSSION

The objective of this study is to demonstrate the viability of omitting surgical intervention on the breast in exceptional responders to NST. Our study aims to evaluate its safety by assessing the non-inferiority of the 5-year DFS of patients with triple-negative, HER2-positive, or ER-low-positive breast cancer who are omitted from breast surgery when predicted to have a pCR after NST based on breast MRI and VAB, compared with that of patients from previous studies who were confirmed to have a pCR after breast surgery. Our primary endpoint will demonstrate if breast surgery is necessary for patients with pCR as predicted by MRI and confirmed by VAB. This has the potential to change the current clinical practice for selected patients who undergo NST.

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The biggest concern of the patients and physicians enrolled in this study would be the false-negative results of VAB in the evaluation of pCR. Phase II trials that evaluated the accuracy of minimally invasive biopsy, including the RESPONDER [21], MICRA [22], and NRG-BR005 trials [23], did not meet the pre-specified FNR or NPV and were terminated after enrolling only a portion of the target accrual. However, the investigators were able to explain the negative results. More than half of the false-negative cases in the RESPONDER trial were methodologically avoidable in terms of the specifications of the biopsy methods and pathological evaluation [21,24]. The MICRA trial was the first to use dynamic contrast-enhanced MRI to assess radiological cCR or partial response. However, in contrast to the RESPONDER trial, NRG-BR005 trial, and other feasibility trials that utilized VAB, the MICRA trial employed core needle biopsy with a 14 G needle to evaluate residual tumors, resulting in insufficient tissue for pathologic assessment [22]. The NRG-BR005 trial resulted in an NPV of 77.5%, which did not meet the primary endpoint of an NPV of 90%. However, a significant proportion of NPVs was due to patients who were HR+/HER2− (21.9%), with an NPV of 46.2% [23]. In a trial conducted by Hayashi et al. [25] in Japan, an NPV of 67.1% was reported. This result can be attributed to the fact that only 13.6% of the patients had a clip marker placed on the primary tumor.

Although prior trials did not meet their primary endpoints of FNR < 10% or NPV ≥ 90%, we were able to identify the factors affecting the accuracy of minimally invasive biopsies in predicting pCR. The stringent inclusion criteria in this trial, according to MRI criteria, microcalcification size, molecular subtype, needle size, utilization of VAB, and pathologic evaluation for the tumor bed, drew upon insights from the feasibility and phase II trials evaluating the accuracy of minimally invasive biopsy in evaluating pCR. Our investigation specifically assessed the impact of omitting breast surgery based on VAB results for pCR in terms of DFS.

While one might argue that a simple lumpectomy of a small area of the residual or clipped lesion is not harmful to the patient, the surgical intervention following the hardships of cytotoxic chemotherapy could be a substantial burden. Patients who underwent lumpectomy reported a relevant reduction in patient-reported QoL. Furthermore, poor patient-reported cosmetic satisfaction was independently associated with impaired QoL, compromised body image, and lower emotional and social functioning [26]. Notably, approximately 50% of patients who underwent lumpectomy and SLNB experienced persistent pain [27]. Consequently, there is a growing trend in the development of surgical methods for breast cancer to minimize invasiveness and reduce surgery-associated morbidities.

Furthermore, there may be concerns about possible undertreatment due to missing residual lesions, which otherwise would have led to further adjuvant treatment, such as capecitabine for TNBC or trastuzumab-emtansine (TDM-1) for HER2-positive breast cancer. However, the KATHERINE trial for HER2-positive breast cancer demonstrated in an exploratory analysis a marginal benefit of adjuvant T-DM1 over trastuzumab for minimal residual disease (ypT1b or less) [28]. In the CREATE-X study, which reported an additional benefit of adjuvant capecitabine in TNBC cases, only a few cases with minimal residual disease were reported [20]. Thus, a distinct analysis was not conducted for this subgroup, precluding any conclusion regarding the benefit of additional treatment after NST in patients with minimal residual TNBC. In addition, ongoing studies on additional adjuvant therapy for residual TNBC after NST are predominantly focused on cases with residual lesions of 1 cm or more. Therefore, the need for additional treatment for minimal residual lesions, which may be overlooked in our study, is expected to be rare [28].

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Recently, promising results were reported by Kuerer et al. [29], showing no recurrence in 31 patients who omitted surgery after being identified as having a pCR on VAB during a follow-up of a median 26.5 months. They also reported patient-reported outcomes and health-related QOL survey results showing an overall positive experience for trial participants, with longitudinal improvements in decisional comfort and overall health-related QOL and minimal lasting adverse effects of therapy [30].

In our study, we will be omitting both breast and axillary surgery for patients who meet a more stringent criteria of post-NST MRI size ≤ 0.5 cm, L-to-B SER ≤ 1.6, cN0 before NST, and no suspicious LN after NST. The safety of omitting axillary surgery in exceptional responders to NST is currently being evaluated in the EUBREAST-01 (NCT04101851, Germany), ASICS (NCT04225858, Netherlands), and ASLAN (NCT04993625, Republic of Korea) trials. In addition, the results of our trial provide insights into the role of axillary surgery in exceptional responders with no evident lymph node involvement before and after NST.

Breast cancer is well characterized according to the expression of HR and HER2, and possesses distinct responsiveness to systemic therapy. Although surgery plays a crucial role in the treatment of relatively indolent luminal subtypes, it may have a limited role in HR-negative or HER2-positive breast cancers that exhibit an exceptional response to NST. Therefore, trials to evaluate the safety of surgical de-escalation in these patients are needed to provide evidence to either avoid overtreatment from unnecessary surgery or prevent the risk of recurrence resulting from the omission of surgery that was deemed necessary. We expect the OPTIMIST trial to provide the first large-scale evidence in this field.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

List of study sites

Supplementary Table 2

The Standard Protocol Items: Recommendations for Interventional Trials 2013 checklist for interventional trials

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