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# Surgical axillary intervention after neoadjuvant systemic therapy (NST) for early-stage breast cancer – Clinical significance of micrometastases: Data from five neoadjuvant studies

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ABSTRACT

*Introduction:* Axillary surgery for early breast cancer has become less aggressive. However, the optimal approach after neoadjuvant systemic therapy (NST) remains uncertain and depends on axillary response. Especially the significance of nodal micrometastases (ypN1mi) after NST regarding oncological outcome remains controversial. Our study retrospectively analyzed ypN1mi occurrence in five neoadjuvant GBG/AGO-B trials from 2012 to 2019.

*Methods:* We analyzed 3211 high-risk early breast cancer patients from five neoadjuvant chemotherapy studies (GeparSepto, GeparOcto, GeparNuevo, GeparX, GeparOla). Patients who underwent breast surgery were analyzed based on type of axillary surgery, ypN1mi incidence, and its correlation with outcome.

*Results:* 98.5% (3163/3211) of patients had breast surgery and axillary information data available. Before NST, 44.1% (1395/3163) had sentinel lymph node biopsy (SLNB), 0.7% (22/3163) underwent axillary lymph node dissection (ALND), and 55.2% (1746/3163) had no axillary surgery. After NST, 65.3% (2057/3150) underwent axillary surgery: SLNB only in 19.4% (612/3150), targeted lymph node biopsy (TLNB) only in 0.2% (5/3150), targeted axillary dissection (TAD) in 0.9% (27/3150), ALND only in 40.9% (1288/3150), and completion ALND following SLNB, TLNB, or TAD in 4.0% (125/3150). Disease-free survival (DFS) was significantly reduced with hazard ratios (HR) of 2.53 (CI 1.63-3.92; $p < 0.001$) for ypN1mi and 2.43 (CI 1.98-3.00; $p < 0.001$) for ypN1

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compared to ypN0. Likewise, HRs for overall survival (OS) were 3.17 (CI 1.77-5.68) for ypN1mi and 3.03 (CI 2.28-4.03) for ypN1.
*Conclusion:* Our data suggest that minimal axillary residuals after NST may affect DFS, DDFS and OS; however, further analysis is needed to assess other variables.

## 1. Introduction

Over the past decades, neoadjuvant systemic therapy (NST) has been the preferred treatment for locally advanced breast cancer. However, it is also increasingly used in operable cases with other high-risk features, such as HER2-positive or triple-negative biology or clinically affected axillary lymph nodes (cN+) [1]. NST offers several advantages, including the ability to reduce the primary tumor stage, decrease the extent of surgical intervention, enhance the rate of breast-conserving procedures, and enable pathologic evaluation of treatment efficacy in individual patients [2].

However, the type of axillary staging surgery that should be offered to patients with breast cancer after NST in distinct clinical situations remains a matter of debate. While sentinel lymph node biopsy (SLNB) is the standard of care for patients with clinically unaffected lymph nodes (cN0), axillary lymph node dissection (ALND) remained the standard for cN + patients for many years longer irrespective of response to NST. Results from several prospective trials displayed increased false-negative rates (FNR) of SLNB alone after NST in initially cN + patients, ranging from 11.9% to 14.2%, and thus above the acceptable threshold of 10% [3–6]. Specific settings were defined (dual tracer marking and harvesting three or more sentinel lymph nodes [SLN]), where the FNR was deemed acceptable [4]. Considering the significantly increased morbidity and reduced quality of life after ALND and the increasing pathological complete response (pCR) rates, further attempts were made to establish techniques to reliably detect axillary residuals after NST in these patients with reduced surgical radicality [7]. Histological verification of pN + via needle biopsy and consecutive clip or seed placement before NST initiation for the use of intraoperative detection after NST was identified as a solution to the clinical dilemma. Targeted resection of clipped lymph nodes (TLNB) combined with SLNB as targeted axillary dissection (TAD) or SLNB alone with dual tracers and three SLN have gradually been implemented in clinical practice years before their implementation in clinical practice guidelines [7,8].

It is of paramount importance to highlight that nowadays, in cN + patients who are planned for NST, axillary staging after NST is primarily a diagnostic procedure and unnecessary harm should be avoided. The presence or absence of nodal metastases in these staging procedures is an important prognostic factor that is used to guide further locoregional and systemic treatment decisions thereby is capable to impact on patients' fate [9–11]. But the cut-off of residual axillary burden for its ability to impact on prognosis and meaningfully guide treatment decisions remains to be identified.

Well-known results from the adjuvant setting have shown that omission of completion ALND (cALND) in patients with limited micro- or macrometastatic lesions in SLNs does not have detrimental effects [12,13]. In these trials, patients who received neoadjuvant therapy were excluded; therefore, no statements guiding further surgical approaches as a consequence of residuals detected with SLNB or TAD after NST can be based on these results. According to current guidelines, in patients with cN + disease at presentation, a persisting axillary tumor should trigger cALND, although the therapeutic effect of this measure is questioned, and prospective trials are investigating its omission [4,14]. The situation remains even less clear in cN0 situations. As comprehensive data are lacking, ALND remains the recommendation for patients with remaining macrometastases and must be discussed on a case-by-case basis in cases involving ypN1mi. However, evaluating the risk of recurrence in patients with ypN1mi is crucial for identifying optimal locoregional and systemic treatment sequences.

## 2. Methods

### 2.1. Study population

Data from 3211 patients with early-stage breast cancer included in the primary analysis of five neoadjuvant GBG/AGO-B trials (GeparSepto, GeparOcto, GeparNuevo, GeparX, and GeparOla) were retrospectively analyzed. Trial designs, pCR rates, and outcome parameters are summarized in Table 1.

Of the 3211 patients included in the primary analysis of five neoadjuvant chemotherapy trials, 48 did not undergo breast surgery after NST and were therefore excluded. Consequently, 3163 patients were retrospectively analyzed: 1192 from GeparSepto, 938 from GeparOcto, 173 from GeparNuevo, 104 from GeparOla, and 756 from GeparX (Fig. 1).

In these five randomized multicenter studies conducted between 2012 and 2019, different anthracycline/taxane-containing neoadjuvant chemotherapy regimens for high-risk early breast cancer were compared. pCR was the primary endpoint in all five trials and all patients with HER2-positive tumors received concurrent trastuzumab and pertuzumab. In GeparSepto, GeparOcto, and GeparX all intrinsic subtypes were eligible. An overview of the five analyzed neoadjuvant chemotherapy studies with detailed information (regimes, eligible subtypes, primary endpoints and pCR rates) are given in Table 1. During the enrollment period of the trials, surgical standards changed, and investigators were allowed to use modern axillary staging approaches even before they were implemented into guidelines. In earlier trials, performing SLNB before NST in patients with unsuspicious lymph nodes at presentation (cN0) was preferred. However, SLNB could be performed before or after NST in all trials. In patients who were clinically lymph node positive at presentation (cN+), axillary staging after NST with SLNB, TAD, or ALND was permitted in all trials. TAD was defined as the resection of an initially clipped TLN conducted simultaneously with SLNB after NST.

All studies were approved by the ethics committees/institutional review boards and competent authorities, and all participants provided written informed consent for the respective analysis.

### 2.2. Clinical and pathological assessment

The analysis was conducted retrospectively on prospectively collected pseudonymized data. Clinical and histopathological data are summarised in Table 2. The variables analyzed were breast and axillary pCR rates, TNM stages, and time to event end points such as disease-free survival (DFS), distant disease-free survival (DDFS), and overall survival (OS). Furthermore, we examined all surgical records to differentiate between the types of surgeries performed before and after NST. Breast pCR was defined as the absence of malignant cells in the primary breast tumor (ypT0). Pathologic findings of macrometastases (>2 mm) or micrometastases (>0.2 mm and/or more than 200 tumor cells, but not more than 2 mm in the largest diameter) were defined as ypN+. Ultrastaging of the lymphnodes was performed according to the local protocols of the participating centers.

### 2.3. Statistical analysis

The time-to-event endpoints were estimated using the Kaplan-Meier product limit method based on pathologic nodal status, and univariate and multivariate (adjusted for cT (1-2 vs 3-4), biological subtype

(HER2-/HR + vs TNBC vs HER2+, Ki67 (cut 20%) und TILs (cut 50%)) Cox proportional hazards regression was used to evaluate the impact of clinical variables on survival outcomes. To address the heterogeneity between studies, a sensitivity analysis was performed adding study as a random effect to the Cox regression. All hazard ratios (HR) shown in the results section are from the univariate models, multivariate and sensitivity analyses results are shown in Table 3. Two-sided $p < 0.05$ was considered statistically significant.

## 3. Results

A total of 3163 of 3211 enrolled patients with early-stage breast cancer underwent breast surgery after NST and were included in this retrospective analysis. The median age of the patients was 49 years. The majority of patients had cT1-2 initial tumor sizes. Most were node-negative at presentation (cN0 = 66.5%) while 29.5% had cN1 and 3.9% had cN2/cN3 disease. Intrinsic subtypes TNBC, HER2-positive, and HR+/HER2-were reported in 38.9%, 29.1%, and 32.0% of the patients, respectively. Most tumors had G3 grading (63.3%). TILs were >50% in 398 patients (12.6%) and ≤50% in 2760 patients (87.4%). A total of 2354 patients were classified as ypN0, 14 as ypN0i+, 56 as ypN1mi, 310 as ypN1, and 196 as ypN2–3. Patients who underwent SLNB prior to NACT without evidence of lymph node involvement and further axillary surgery after NACT were included in our analysis and classified as ypN0. In contrast, patients with abnormal lymph nodes at baseline who did not undergo additional lymph node surgery after NACT were excluded from the analysis. This explains the difference between the 3163 patients who underwent lymph node surgery and the 2930 patients included in the ypN stage distribution shown in Table 2. The baseline characteristics of the ypN0 and ypN1mi cohorts differ greatly in some areas and are similar in others. The age structure at initial diagnosis is very similar in both cohorts. Over 60% of patients received their initial diagnosis between the ages of 40 and 60. In addition, most patients in both cohorts had ductal invasive tumors. Characteristics in which the two cohorts displayed relevant differences were cT stage, cN stage, and intrinsic subtype. In the ypN1mi cohort, only 23% initially had cT1, while in the ypN0 cohort 42% had cT1. In addition, higher tumor stages (cT3-cT4) were more common in the ypN1mi cohort than in the ypN0 cohort, as were cT3 14.3% vs. 5.8%, and for cT4 9.0% vs. 2.9%. Only 37.0% in the ypN1mi cohort as opposed to 74.3% of the ypN0 cohort initially had clinically negative lymph nodes. 53.7% of patients with ypN1mi and 23.2% with ypN0 had initially cN1 nodes. An initial cN2-3 nodal status was observed in 9.3% of patients with ypN1mi but only in 2.6% of those with ypN0. With regard to intrinsic subtypes, it is notable that in the ypN1mi group, the majority of the patients (58.9%) had HR+/HER2-tumors, whereas in the ypN0 group, only 23.4% had this subtype. An overview of baseline characteristics is shown in Table 2.

Prior to NST, 44.1% (1395/3163) of patients underwent sentinel lymph node biopsy. 55.2% (1746/3163) did not undergo axillary surgery prior to NST. Following NST, lymphnode surgery type is known in 2057 patients: 19.4% (612/3150) had SLNB only, 0.2% (5/3150) received TLNB only, 0.9% (27/3150) had TAD, and 40.9% (1288/3150) had ALND only. Additionally, 4.0% (125/3150) of patients underwent cALND following SLNB, TLNB, or TAD. In 13 patients, information on axillary surgical procedure after NST was unknown (in 5 also unknown if it was performed, in 8 only the type of the performed lymphnode surgery).

Of the 2065 patients who underwent lymph node surgery after NST, ypN and ypT status was not available for 10 and 9 patients.

Patients with any surgery after NST and initial cN0 status had ypN0 in 83.4% (892/1069) of cases, whereas patients with initial cN + had ypN0 in 60.5% (581/960) of cases. A total of 43.1% (879/2038) had a pathological complete response in the breast, with only 5.3% (47/879) of these exhibiting concurrent residual disease in the lymph nodes (ypT0, ypN+). In patients with breast pCR, rates for ypN0 according to subtype were 98.6% for patients with HER2-positive, 94.6% for triple-negative, and 84.2% for HR+/HER2-subtypes, respectively. Patients with breast pCR were further analyzed according to their initial clinical nodal status. Patients with cN+ and breast pCR also displayed fairly high rates of ypN0 compared to those with cN0; 97.8% vs. 99.4% for HER2-positive, 88.3% vs. 98.0% for triple-negative, and 83.1% vs. 85.1% for HR+/HER2-tumors.

At axillary surgery after NST, only 0.7% (14) and 2.7% (56) of 2038 patients with any lymph node surgery after NST had ypN0i+ and

**Table 1**
Overview of the five analyzed neoadjuvant chemotherapy studies by AGO and GBG.

| | N (primary analysis of the trial) | N (analyzed) | Included subtypes | Trial designs | pCR rates (ypT0, ypN0) |
|---|---|---|---|---|---|
| **GeparSepto (2012–2013 recruited)** | 1206 | 1192 | cT2-cT4a-d, including inflammatory breast cancer or a clinical stage T1c plus 1 additional high-risk factor (axillary node involvement, ER- and PR- receptor-negative disease, Ki-67 > 20%, or HER2 overexpression) | 12x nabPac q1w ± TP[a]→4x EC q3w ± TP[a] vs 12x Pac q1w ± TP[a]→4x EC q3w ± TP[a] | nab-paclitaxel group 38% (95% CI 35-42) vs. paclitaxel group 29% (95% CI 25-33); OR 1.53 (95% CI 1.20-1.95), unadjusted p = 0.00065 |
| **GeparOcto (2014–2016 recruited)** | 945 | 938 | cT1c-cT4a-d HER2-positive or TNBC (irrespective of nodal status, luminal B-like tumors only if pN+) | 18 x NPLD/Pac±Carbo[b] q1w or TP[a] vs 3x Eq2w → 3x Pac q2w ± TP[a]→ 3x C q2w ± TP[a] | iddEPC group 48.3% (95% CI 43.7-52.9), with PM(Cb) 48.0% (95% CI 43.4-52.6), respectively (PM(Cb) versus iddEPC odds ratio 0.99 (95% CI 0.77-1.28), p = 0.979 |
| **GeparNuevo (2016–2017 recruited)** | 174 | 173 | cT2-cT4a-d non-metastatic invasive TNBC | 12x nabPac q1w + Durva → 4x EC q2w + Durva vs. 12x nabPac q1w + Placebo → 4x EC q2w + Placebo | durvalumab 53.4% (95% CI 42.5% to 61.4%) vs. placebo 44.2% (95% CI 33.5% to 55.3%; unadjusted continuity corrected $\chi^2$ p = 0.287), corresponding to OR = 1.45 (95% CI 0.80–2.63, unadjusted Wald p = 0.224) |
| **GeparX (2017–2019 recruited)** | 780 | 756 | cT2-cT4a-d or cT1c, with either clinically node-positive or pathologically node-positive or HR-negative disease, or Ki-67 > 20%, or HER2-positive | 12x nabPac±Carbo[b] q1w ± TP[a]→ EC q2w/q3w vs 4x nabPac d1+8 q3w ± Carbo[b] q1w ± TP[a]→ EC q2w/q3w | 41.0% (90% CI, 37% to 45%) with denosumab vs 42.8% (90% CI, 39% to 47%) (p = 0.58) without denosumab |
| **GeparOla (2016–2018 recruited)** | 106 | 104 | HER2-negative cT2-cT4a-d or cT1c with either cN + or pNSLN + or cT1c and TNBC or cT1c and Ki-67 > 20% with HRD | 12x Pac q1w + Ola → ECq2w/q3w vs 12x Pac + Carbo q1w → ECq2w/q3w | 55.1% (90% CI 44.5% to 65.3%) vs. PCb 48.6% (90% CI 34.3% to 63.2%) |

nabPac – nab-Paclitaxel; Pac – Paclitaxel; EC – Epirubicin/Cyclophosphamid; Durva – Durvalumab; Carbo – Carboplatin; Ola - Olaparib.
[a] For HER2-positive BC.
[b] For TNB C.

ypN1mi axillary stage. Only 0.15% (3) and 0.64% (13) had ypN0i+ and ypN1mi as the sole residual diseases without the simultaneous presence of invasive breast residuals. The median follow-up time was 67 months. DFS was significantly lower for patients with axillary residuals including ypN1mi but not for ypN0i + compared to ypN0 [univariate HRs 2.17 (CI 0.81-5.81; p = 0.123) for ypN0i+, 2.53 (CI 1.63-3.92; p < 0.001) for ypN1mi, and 2.43 (CI 1.98-3.00; p < 0.001) for ypN1]. Estimated 5-year DFS rates were 83.4% (95% CI 81.8-85.0) for ypN0, 69.2% (95% CI 37.3-87.2) for ypN0i+, 58.5% (95% CI 43.3-71.0) for ypN1mi, and 61.4% (95% CI 55.2-67) for ypN1. When analyzing OS, patients with any axillary residuals, including ypN0i+, displayed a worse prognosis compared to those with ypN0 [HRs 4.98 (CI 1.85-13.4; p = 0.001) for ypN0i+, 3.17 (95% CI 1.77-5.68, p < 0.001) for ypN1mi, and 3.03 (CI 2.28-4.03, p < 0.001) for ypN1]. Estimated 5-year OS rates were 92.7% (95% CI 91.4-93.7) for ypN0, 64.1% (95% CI 28.2-85.5) for ypN0i+, 81.2% (95% CI 66.9-89.8) for ypN1mi, and 79% (95% CI 73.5-83.4) for ypN1. DDFS was significantly lower for patients with axillary residuals including ypN0(i+) and ypN1mi compared to ypN0 [HRs 2.88 (CI 1.07-7.71; p = 0.036) for ypN0i+, 2.80 (95% CI 1.74-4.50, p < 0.001) for ypN1mi, and 2.76 (CI 2.20-3.45, p < 0.001) for ypN1]. Estimated DDFS rates were 87.1% (95% CI 85.6-88.5) for ypN0, 69.2% (95% CI 37.3-87.2) for ypN0i+, 62.6% (95% CI 47.3-74.6) for ypN1mi, and 66.2% (95% CI 60.1-71.5) for ypN1 (Figs. 2–4, Table 3). Multivariate models and sensitivity analyses adjusted for study provided similar results for all three survival endpoints (Table 3).

## 4. Discussion

According to our data, remaining micrometastases in the axilla after NST might impact disease-free, distant disease-free and overall survival

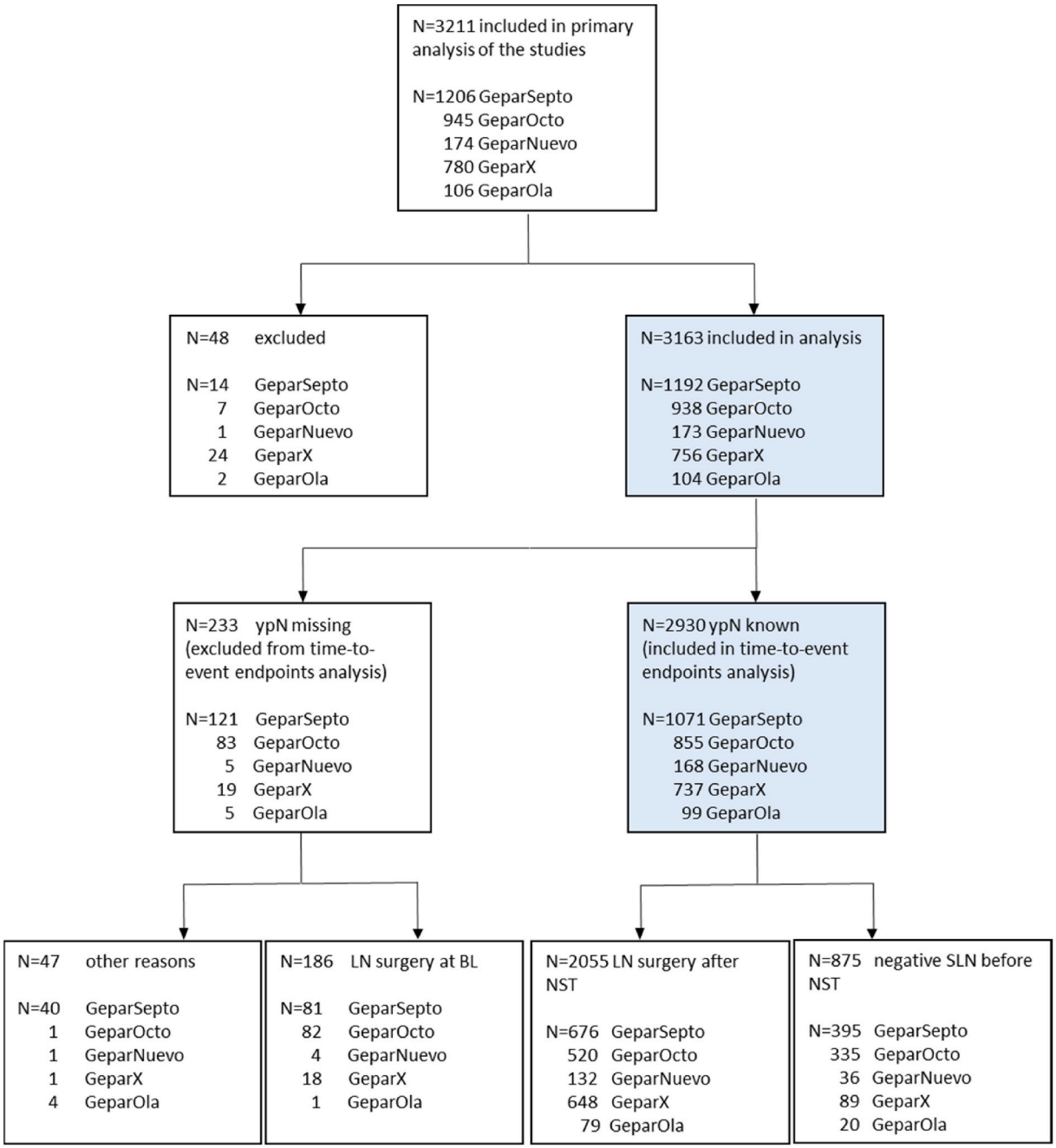



**Fig. 1.** Study flowchart.

in patients that have received anthracycline/taxane based NST [HR DFS 2.53 (95% CI 1.63-3.91; p < 0.001), DDFS 2.8 (95% CI 1.74-4.5; p < 0.001) and OS 3.17 (95% CI 1.77-5.68; p < 0.001) for ypN1mi compared to ypN0].

As seen in prior analyses, we observed a variation in axillary response rates between the intrinsic subtypes [15]. All patients with HER2-positive primary tumors included in our study received concurrent trastuzumab and pertuzumab together with NST and had very high rates of axillary pCR in case of breast pCR irrespective of the initial nodal status. A maximum of 2% of patients with cN0 and breast pCR following NST for TNBC or HER2-positive BC had nodal residuals. Axillary staging following highly effective NST is very unlikely to reveal treatment relevant information in this population and this observation supports trials like EUBREAST01 (NCT04101851) investigating the complete omission of axillary staging in this clinical situation [16]. Conversely, patients with HR+/HER2-primary tumors had the lowest ypN0 rates, which was irrespective of initial cN status. There is an ongoing debate about whether insufficient assessment of axillary lymph node status after neoadjuvant therapy leads to loss of critical prognostic information and, in turn, to suboptimal selection or delivery of post-neoadjuvant treatments like ribociclib, abemaciclib or olaparib. Kuehn et al. reported results from the prospective AXSANA/EUBREAST 03 (R) trial (NCT04373655) evaluating how performing diagnostic cALND after NACT influences treatment decisions in patients who have isolated tumor cells or micrometastases in the SLN or TLN. In this trial (5329 patients overall; 2194 planned for SLNB/TAD/TLNB), 71 patients had ypN1mi in the SLN/TLN, and although cALND upstaged 6 of them (5 to ypN2, 1 to ypN3), this did not change their post-NACT treatment because none had achieved a breast pCR [17].

Observations concerning the prognostic impact of ypN1mi similar to our study results, have been previously reported by Wong et al. In this retrospective cohort study, 967 patients that had NST for cT1-4, cN0-1 breast cancer were analyzed according to pathologic nodal status following NST and its impact on DFS and OS was estimated. They reported a significantly lower DFS for patients with residual micrometastases compared to those classified as ypN0 after NST with a HR of 2.14 (95% CI 1.20-3.81) and estimated five-year DFS rates of 74.7% and 88.4% respectively. Additionally, estimated five-year overall survival decreased with a higher residual nodal burden: ypN0 at 88.9%, ypN1mi at 79.5%, and ypN1 at 77.6% (p < 0.001) [18]. This is well in line with our findings.

A different retrospective cohort study evaluated the impact of axillary residuals on DFS and OS among exclusively clinically node-positive breast cancer patients undergoing NST. Survival of patients with axillary pathologic complete response, those with residual axillary isolated tumor cells or micrometastases (ypN0i+/ypN1mi), and patients with residual axillary macrometastases (ypN1-3) were compared. In contrast to our results, van Nijnatten and colleagues [19] found comparable DFS and OS for ypN0 and ypN0i+/ypN1mi (HR 1.38 (0.40-4.79, p = 0.613) and HR 0.92 (0.27-3.09, p = 0.889), respectively), but significant differences were noted between ypN0 and ypN1-3 (HR 1.78 (1.06-3.00, p = 0.031) and HR 1.70 (1.07-2.71, p = 0.026), respectively). It is not clear whether the prognosis for patients with residual micrometastases following NST varies depending on their initial clinical lymph node status, but this is of importance. Minimal axillary residuals in an individual that has had extensive disease prior to NST, may as well be a sign of good response to systemic treatment, whereas in a patient with cN0, it is a sign of resistance to the applied treatment. As van Nijnjatten et al.

**Table 2**
Patient and tumor characteristics at baseline by ypN.

| Parameter | Parameter value | Overall N (%) | ypN0 N (%) | ypN0i+ N (%) | ypN1mi N (%) | ypN1 N (%) | ypN2-3 N (%) | ypNx missing N (%) |
|---|---|---|---|---|---|---|---|---|
| Overall | | 3163 | 2354 | 14 | 56 | 310 | 196 | 233 |
| Age at diagnosis, years | <30% | 101 (3.2) | 88 (3.7) | 0 (0.0) | 2 (3.6) | 7 (2.3) | 1 (0.5) | 3 (1.3) |
| | 30- <40 | 551 (17.4) | 407 (17.3) | 1 (7.1) | 10 (17.9) | 53 (17.1) | 32 (16.3) | 48 (20.6) |
| | 40- <50 | 1060 (33.5) | 779 (33.1) | 6 (42.9) | 18 (32.1) | 110 (35.5) | 64 (32.7) | 83 (35.6) |
| | 50- <60 | 897 (28.4) | 669 (28.4) | 3 (21.4) | 16 (28.6) | 89 (28.7) | 55 (28.1) | 65 (27.9) |
| | 60- <70 | 465 (14.7) | 358 (15.2) | 3 (21.4) | 8 (14.3) | 39 (12.6) | 34 (17.3) | 23 (9.9) |
| | 70+ | 89 (2.8) | 53 (2.3) | 1 (7.1) | 2 (3.6) | 12 (3.9) | 10 (5.1) | 11 (4.7) |
| | missing | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cT at diagnosis | cT1 | 1219 (38.7) | 979 (41.8) | 3 (21.4) | 13 (23.2) | 94 (30.5) | 37 (19.0) | 93 (40.1) |
| | cT2 | 1576 (50.0) | 1163 (49.6) | 7 (50.0) | 30 (53.6) | 157 (51.0) | 96 (49.2) | 123 (53.0) |
| | cT3 | 228 (7.2) | 136 (5.8) | 2 (14.3) | 8 (14.3) | 33 (10.7) | 37 (19.0) | 12 (5.2) |
| | cT4a-c | 52 (1.7) | 27 (1.2) | 0 (0.0) | 3 (5.4) | 9 (2.9) | 12 (6.2) | 1 (0.4) |
| | cT4d | 74 (2.3) | 39 (1.7) | 2 (14.3) | 2 (3.6) | 15 (4.9) | 13 (6.7) | 3 (1.3) |
| | missing | 14 | 10 | 0 | 0 | 2 | 1 | 1 |
| cN at diagnosis | cN0 | 2079 (66.5) | 1732 (74.3) | 8 (61.5) | 20 (37.0) | 106 (34.5) | 51 (26.2) | 162 (72.6) |
| | cN1 | 922 (29.5) | 540 (23.2) | 3 (23.1) | 29 (53.7) | 182 (59.3) | 111 (56.9) | 57 (25.6) |
| | cN2 | 85 (2.7) | 39 (1.7) | 1 (7.7) | 3 (5.6) | 15 (4.9) | 24 (12.3) | 3 (1.3) |
| | cN3 | 38 (1.2) | 21 (0.9) | 1 (7.7) | 2 (3.7) | 4 (1.3) | 9 (4.6) | 1 (0.4) |
| | missing | 39 | 22 | 1 | 2 | 3 | 1 | 10 |
| Intrinsic subtype | HR+/HER2- | 1013 (32.0) | 551 (23.4) | 8 (57.1) | 33 (58.9) | 198 (63.9) | 138 (70.4) | 85 (36.5) |
| | TNBC | 1229 (38.9) | 1029 (43.7) | 5 (35.7) | 15 (26.8) | 77 (24.8) | 41 (20.9) | 62 (26.6) |
| | HER2+ | 921 (29.1) | 774 (32.9) | 1 (7.1) | 8 (14.3) | 35 (11.3) | 17 (8.7) | 86 (36.9) |
| | missing | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Grading | G1 | 57 (1.8) | 38 (1.6) | 3 (21.4) | 1 (1.8) | 7 (2.3) | 5 (2.6) | 3 (1.3) |
| | G2 | 1105 (34.9) | 736 (31.3) | 5 (35.7) | 25 (44.6) | 141 (45.5) | 99 (50.5) | 99 (42.5) |
| | G3 | 2001 (63.3) | 1580 (67.1) | 6 (42.9) | 30 (53.6) | 162 (52.3) | 92 (46.9) | 131 (56.2) |
| | missing | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Histological tumour type | ductal invasive | 2753 (87.0) | 2057 (87.4) | 10 (71.4) | 51 (91.1) | 274 (88.4) | 165 (84.2) | 196 (84.1) |
| | lobular invasive | 71 (2.2) | 33 (1.4) | 2 (14.3) | 3 (5.4) | 13 (4.2) | 9 (4.6) | 11 (4.7) |
| | other | 339 (10.7) | 264 (11.2) | 2 (14.3) | 2 (3.6) | 23 (7.4) | 22 (11.2) | 26 (11.2) |
| | missing | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ki67, % | ≤20% | 579 (18.3) | 378 (16.1) | 5 (35.7) | 14 (25.0) | 76 (24.5) | 54 (27.6) | 52 (22.3) |
| | >20% | 2584 (81.7) | 1976 (83.9) | 9 (64.3) | 42 (75.0) | 234 (75.5) | 142 (72.4) | 181 (77.7) |
| | missing | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Stromal TILS, % | TILs≤50 | 2760 (87.4) | 2018 (85.9) | 13 (92.9) | 54 (96.4) | 287 (92.6) | 183 (93.4) | 205 (88.0) |
| | TILs> 50% | 398 (12.6) | 331 (14.1) | 1 (7.1) | 2 (3.6) | 23 (6.6) | 13 (6.6) | 28 (12.0) |
| | missing | 5 | 5 | 0 | 0 | 0 | 0 | 0 |

**Table 3**
Estimated 5-year DFS, DDFS and OS rates by ypN and HR by Cox regression.

| Endpoint | ypN0 | 95% CI, ypN0 | ypN0i+ | 95% CI, ypN0i+ | ypN1mi | 95% CI, ypN1mi | ypN1 | 95% CI, ypN1 | ypN2-3 | 95% CI, ypN2-3 |
|---|---|---|---|---|---|---|---|---|---|---|
| **DFS** | | | | | | | | | | |
| 5-year rates | 83.4% | (81.8%, 85.0%) | 69.2% | (37.3%, 87.2%) | 58.5% | (43.3%, 71.0%) | 61.4% | (55.2%, 67.0%) | 47.6% | (40.2%, 54.6%) |
| HR, univariate | ref | | 2.17 | (0.81, 5.81) | 2.53 | (1.63, 3.92) | 2.43 | (1.98, 3.00) | 4.06 | (3.28, 5.02) |
| HR, multivariate[a] | ref | | 2.18 | (0.81, 5.85) | 2.55 | (1.64, 3.97) | 2.57 | (2.06, 3.21) | 4.09 | (3.20, 5.23) |
| HR, adjusted for study | ref | | 2.20 | (0.82, 5.90) | 2.60 | (1.68, 4.04) | 2.45 | (1.99, 3.02) | 4.07 | (3.29, 5.04) |
| **DDFS** | | | | | | | | | | |
| 5-year rates | 87.1% | (85.6%, 88.5%) | 69.2% | (37.3%, 87.2%) | 62.6% | (47.3%, 74.6%) | 66.2% | (60.1%, 71.5%) | 51.2% | (43.7%, 58.2%) |
| HR, univariate | ref | | 2.88 | (1.07, 7.71) | 2.80 | (1.74, 4.50) | 2.76 | (2.20, 3.45) | 4.76 | (3.79, 5.97) |
| HR, multivariate[a] | ref | | 2.82 | (1.05, 7.58) | 2.72 | (1.68, 4.39) | 2.79 | (2.19, 3.55) | 4.41 | (3.40, 5.73) |
| HR, adjusted for study | ref | | 2.88 | (1.07, 7.72) | 2.81 | (1.75, 4.52) | 2.76 | (2.21, 3.45) | 4.76 | (3.79, 5.97) |
| **OS** | | | | | | | | | | |
| 5-year rates | 92.7% | (91.4%, 93.7%) | 64.1% | (28.2%, 85.5%) | 81.2% | (66.9%, 89.8%) | 79.0% | (73.5%, 83.4%) | 62.2% | (54.4%, 69.0%) |
| HR, univariate | ref | | 4.98 | (1.85, 13.4) | 3.17 | (1.77, 5.68) | 3.03 | (2.28, 4.03) | 5.65 | (4.28, 7.45) |
| HR, multivariate[a] | ref | | 4.95 | (1.83, 13.4) | 3.13 | (1.73, 5.65) | 3.27 | (2.40, 4.44) | 5.72 | (4.14, 7.92) |
| HR, adjusted for study | ref | | 5.17 | (1.92, 14.0) | 3.35 | (1.86, 6.02) | 3.05 | (2.29, 4.06) | 5.66 | (4.29, 7.47) |

[a] Adjusted for cT (1-2 vs 3-4), biological subtype (HER2-/HR + vs TNBC vs HER2+, Ki67 (cut >20%) und TILs (cut >50%).

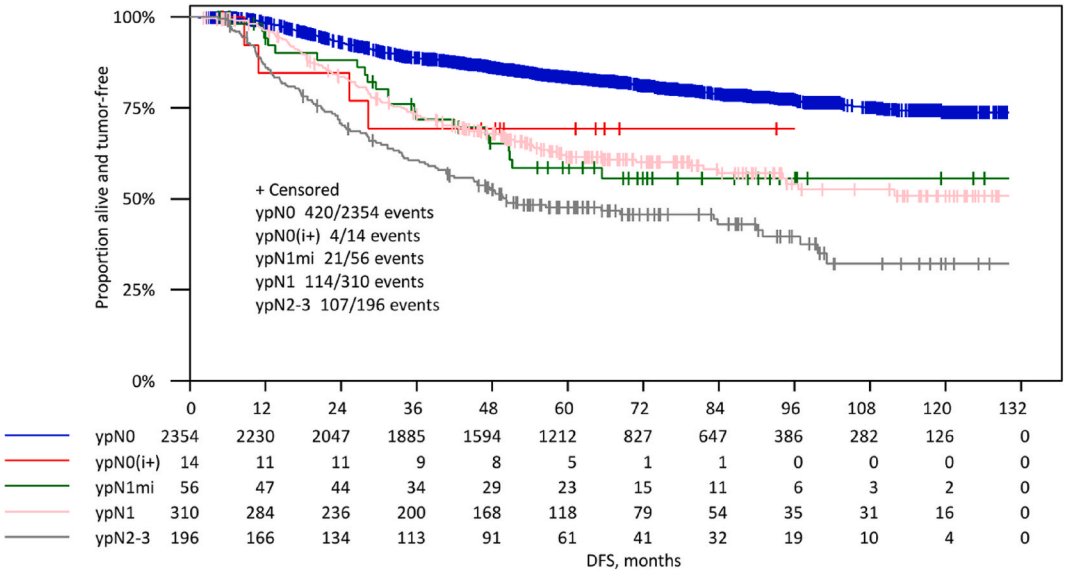



**Fig. 2.** Kaplan-Meier DFS analyses by ypN.

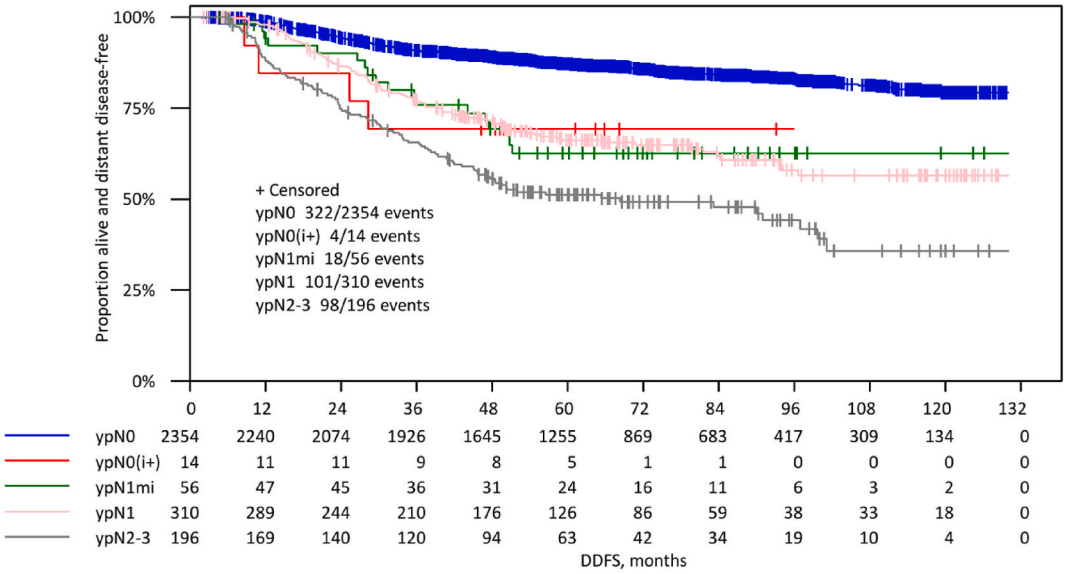



**Fig. 3.** Kaplan-Meier DDFS analyses by ypN.

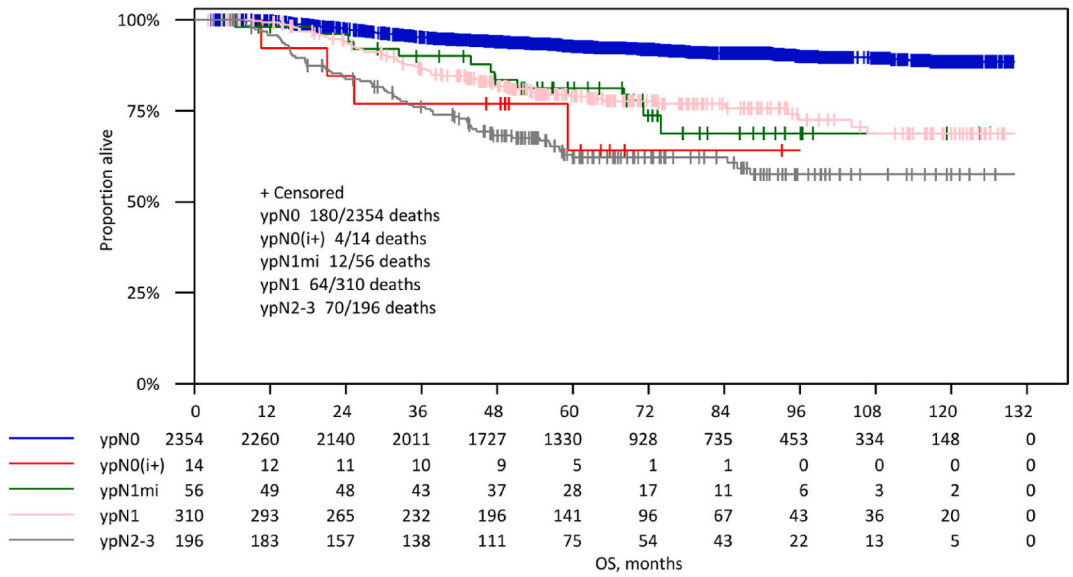



**Fig. 4.** Kaplan-Meier OS analyses by ypN.

have only included patients with initially affected nodes, this may have contributed to the observed differences compared to our results. Moreover, in this analysis a much lower proportion of triple negative disease was included with 18.5% as opposed to 38.9% in our cohort. Since we have shown that response rates in the axilla vary significantly depending on the subtype, careful interpretation of such findings is required, and the axillary stage alone should not be interpreted without considering the clinical context of other baseline characteristics.

Several studies have shown that cALND reveals additional nodal metastases in up to 17-30% of patients with ITCs and in 50-64% of those with micrometastases in the SLN/TLN [20,21].

Nevertheless, since all patients in van Ninjatten's cohort received ALND, an undiscovered, remaining higher nodal burden in ypN1mi patients as cause of an impaired survival is rather unlikely.

At first glance, the poorer prognosis of patients with residual micrometastases may simply reflect underlying resistance to the administered chemotherapy and the adverse prognostic effect of non-response to NST [22]. On the other hand, remaining micrometastatic disease in cN0 patients might as well be an indicator of initial understaging. Various prospective randomized phase 3 studies investigating SLNB prior to NST have proven clinical evaluation as cN0 to be wrong in about every fourth patient [23–25]. Furthermore, it should be noted that it is difficult to determine the nodal status after NST. As most recently presented [26], clinical evaluation of ycN status including axillary ultrasound after NST should not guide decisions when choosing the surgical approach, because the clinical evaluation is at least in one third of the cases untrue. The authors state that 36% of patients with ycN + had a postoperative stage of ypN0 and the same number of patients with ycN0 turned out to harbor lymph node metastases.

Further factors that may have influenced outcomes include the extend of received surgical and radiotherapy treatment, the type of NST administered, the extend of the disease at diagnosis as well as the intrinsic subtype. Moreover, the presence of ERpos disease and thereby applicability of adjuvant ET, the availability of adjuvant HER2 directed treatment and postneoadjuvant treatments like T-DM1 or capecitabine are able to influence patients' prognosis after assessment of ypN status following NST. The impact of these factors cannot be clearly separated, which is a limitation of these retrospective studies including our own.

A clear strength of our study is the collection of prospective data in large scale randomized multicenter trials providing uniform data. All patients received very comparable and highly effective anthracycline/taxane based chemotherapies. In case of HER2-positive disease, all patients received neoadjuvant trastuzumab and pertuzumab concurrent with chemotherapy.

The additional benefit of cALND potentially detecting further macrometasases after having found limited axillary residuals compared to axillary radiotherapy remains to be answered.

Several studies suggest that omission of ALND may be oncologically safe in selected ypN1mi patients, particularly when regional nodal irradiation (RNI) is administered. The large international OPBC-07/microNAC cohort study also demonstrated very low 3 years axillary recurrence rates (2.0%) in patients with ypN1mi disease, with no significant difference between those undergoing ALND and those managed without ALND. The majority (79.9%) of whom received nodal radiotherapy. Multivariable analysis showed that triple-negative breast cancer (hazard ratio 3.83, 95% CI 1.72–8.52) and omission of nodal radiotherapy (2.62, 95% CI 1.19–5.73) were each independently associated with a higher risk of axillary recurrence, regardless of whether an ALND was performed [21]. Available evidence, such as the aforementioned OPBC-07/microNAC cohort study, suggests that regional nodal irradiation (RNI) may provide adequate locoregional control in this subgroup, potentially allowing omission of completion axillary lymph node dissection (ALND) [21]. Analyses such as those in the AMAROS trial demonstrate no significant overall survival benefit associated with more extensive locoregional treatment in patients with a positive sentinel node biopsy, suggesting that this observation may be applicable to patients with micrometastatic nodal disease [27]. These findings support the concept that ypN1mi represents a low-volume residual disease state, in which the therapeutic benefit of additional surgical intervention may be limited. Moreover, RNI has consistently been shown to reduce locoregional recurrence in node-positive early breast cancer, although its impact on overall survival in the context of contemporary systemic therapy remains less clear. However, data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that regional node radiotherapy significantly reduced breast cancer mortality and overall mortality in a meta-analysis of studies conducted after the 1980s [28]. Importantly, the absence of prospective randomized trials specifically addressing ypN1mi limits the strength of current recommendations. Results from the prospective randomized Alliance A11202 trial (NCT01901094), which is comparing completion ALND with axillary radiotherapy in patients with clinically occult nodal disease after NACT, are still awaited. Taken together, the available data support a de-escalated approach in selected patients with ypN1mi, favoring RNI in combination with effective systemic therapy while

avoiding the morbidity associated with ALND; however, treatment decisions should be individualized based on tumor biology, extent of residual disease, and multidisciplinary assessment.

One of the study's strengths is the sample size of 3163 patients included in this analysis. However, only 56 of these patients had ypN1mi as final axillary stage which highlights the complexity of investigating this situation. A by far larger cohort of patients with micrometastases would be most desirable. Remaining isolated tumor cells were even less frequent, which does not allow to draw conclusions for this cohort in our study.

Axillary surgery in breast cancer is used for staging and treatment puposes. Less invasive alternatives to ALND are needed to reliably identify higher-risk patients within patients with low-volume nodal involvement.

What potential strategies can be expected in the future to better stratify patients for the appropriate axillary surgery? Establishing a reliable biomarker that can accurately estimate nodal disease burden would support more precise choice of axillary surgical strategy. Data from the I-SPY2 trial demonstrated that post-NST ctDNA status showed a strong, statistically significant association with ypN category. Negative ctDNA after NAST was linked to a very low risk of ypN2 disease, suggesting that these patients are particularly suitable for SLNB surgery or TAD [29].

In summary, we suggest that micrometastatic axillary residuals after NST may have an impact on DFS, DDFS and OS. Furthermore, our data indicates that risk of distant recurrence and deaths is most relevant also to patients with ypN1mi with hazard ratios indicating a 2.5-fold increased risk of recurrence, a 3-fold increase in the risk for an OS event for ypN1mi compared to ypN0, respectively. Detection of ypN1mi possibly indicates sufficient risk of distant recurrence, warranting to focus on effective post-NST systemic treatments and radiotherapy in lieu of further surgical treatment as still recommended by international guidelines to this day. Nevertheless, our data support further research to assess the impact of other variables.

## Ethical statement

Approval was not required for this paper. For the reported trials, all procedures were performed in compliance with relevant laws and institutional guidelines and have been approved by the appropriate institutional committees separately.

## Data sharing statement

| | |
|---|---|
| Will individual participant data be available (including data dictionaries)? | Yes |
| What data in particular will be shared? | Individual participant data that underlie the results reported in this article, after final analysis and publication of all secondary efficacy endpoints |
| What other documents will be available? | Study protocol; Statistical report (if necessary for the project) |
| When will data be available (start and end dates)? | Beginning after final analysis and publication of all secondary efficacy endpoints; no end date |
| With whom? | Researchers who provide translational research proposals. Proposals should be approved by the GBG scientific board. |
| For what types of analyses? | To achieve aims in the approved proposal |
| By what mechanism will data be made available? | Proposals should be directed to http://www.gbg.de/de/forschung/translationale-forschung.php; to gain access, data requestors will need to sign a data transfer agreement |

## Trial registration

GeparSepto (NCT01583426), GeparOcto (NCT02125344), GeparNuevo (NCT02685059), GeparX (NCT02682693), GeparOla (NCT02789332).

## Prior presentation

Poster presented at ESMO Breast Cancer Congress, 2024, Berlin.

## Role of funding source

The GeparSepto study was funded by BMS (Celgene) and Roche; the GeparOcto trial was financially supported by Amgen, Roche, TEVA and Vifor; the GeparNuevo trial was financially supported by AstraZeneca, and the drug was supported by AstraZenca and BMS (Celgene); the GeparX trial was financially supported by Amgen and BMS (Celgene); the GeparOla study was financially supported by AstraZeneca.

## CRediT authorship contribution statement

**Fabienne J. Warnecke:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Johannes Holtschmidt:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Andreas Schneeweiss:** Validation, Writing – review & editing. **Peter A. Fasching:** Validation, Writing – review & editing. **Michael Untch:** Validation, Writing – review & editing. **Theresa Link:** Validation, Writing – review & editing. **Sabine Schmatloch:** Validation, Writing – review & editing. **Mattea Reinisch:** Validation, Writing – review & editing. **Peter Klare:** Validation, Writing – review & editing. **Carsten Denkert:** Validation, Writing – review & editing. **Marianne Just:** Validation, Writing – review & editing. **Vesna Bjelic-Radisic:** Validation, Writing – review & editing. **Claus Hanusch:** Validation, Writing – review & editing. **Jens-Uwe Blohmer:** Validation, Writing – review & editing. **Christoph Salat:** Validation, Writing – review & editing. **Kristina Lübbe:** Validation, Writing – review & editing. **Jens Huober:** Validation, Writing – review & editing. **Kerstin Rhiem:** Validation, Writing – review & editing. **Valentina Nekljudova:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing. **Sibylle Loibl:** Conceptualization, Funding acquisition, Methodology, Resources, Validation, Writing – review & editing. **Christine Solbach:** Conceptualization, Methodology, Validation, Writing – review & editing.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: FJW reports administrative support, equipment, drugs, or supplies, statistical analysis, travel, and writing assistance were provided by GBG Forschungs GmbH. JHo, VN, SL reports financial support was provided by GBG Forschungs GmbH as employees. JHo reports a relationship with Daiichi Sankyo Europe GmbH that includes: funding grants and non-financial support. JHo reports a relationship with Hologic that includes: funding grants. JHo reports a relationship with MSD Oncology that includes: non-financial support. JHo reports a relationship with Novartis that includes: funding grants. JHo reports a relationship with Palleos Health Care that includes: funding grants. JHo reports a relationship with Pfizer that includes: funding grants. JHo reports a relationship with Roche Pharma that includes: funding grants. JHo reports a relationship with Seagen that includes: funding grants. AS reports a relationship with Celgene that includes: consulting or advisory, funding grants, and travel reimbursement. AS reports a relationship with Roche that includes: consulting or advisory, funding grants, and travel

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reports a relationship with Lilly that includes: consulting or advisory and speaking and lecture fees. J-UB reports a relationship with Novartis that includes: consulting or advisory and speaking and lecture fees. J-UB reports a relationship with Pfizer that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. J-UB reports a relationship with Roche that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. J-UB reports a relationship with Seagen that includes: consulting or advisory and speaking and lecture fees. KL reports a relationship with AstraZeneca that includes: consulting or advisory and speaking and lecture fees. KL reports a relationship with Daiichi Sanyko that includes: consulting or advisory and speaking and lecture fees. KL reports a relationship with Eisai that includes: consulting or advisory and speaking and lecture fees. KL reports a relationship with Exact Sciences that includes: consulting or advisory and speaking and lecture fees. KL reports a relationship with Lilly that includes: consulting or advisory and speaking and lecture fees. KL reports a relationship with MSD that includes: consulting or advisory and speaking and lecture fees. KL reports a relationship with Novartis that includes: consulting or advisory and speaking and lecture fees. KL reports a relationship with Pfizer that includes: consulting or advisory and speaking and lecture fees. KL reports a relationship with Roche that includes: consulting or advisory and speaking and lecture fees. KL reports a relationship with Seagen that includes: consulting or advisory and speaking and lecture fees. JHu reports a relationship with Lilly that includes: consulting or advisory and funding grants. JHu reports a relationship with Novartis that includes: consulting or advisory and funding grants. JHu reports a relationship with Roche that includes: consulting or advisory, funding grants, and travel reimbursement. JHu reports a relationship with Pfizer that includes: consulting or advisory and funding grants. JHu reports a relationship with AstraZeneca that includes: consulting or advisory, funding grants, and travel reimbursement. JHu reports a relationship with Gilead that includes: consulting or advisory, funding grants, and travel reimbursement. JHu reports a relationship with Daiichi Sankyo that includes: consulting or advisory, funding grants, and travel reimbursement. JHu reports a relationship with Menarini Stemline that includes: funding grants. JHu reports a relationship with MSD that includes: funding grants. JHu reports a relationship with Abbvie that includes: consulting or advisory and funding grants. SL has received funds for consulting or advisory role from Pfizer, Roche, Novartis, Seattle Genetics, Lilly, AstraZeneca/MedImmune, Bristol-Myers Squibb, Abbvie, Amgen, Diiachi Sankyo, GlaxoSmithKline, Eisai Europe, Relay Therapeutics, Sanofi, Olema Pharmaceuticals, Menarini Group, MSD Oncology, BeiGene, Bicycle Therapeutics, BMS, Jazz Pharmaceuticals (paid to GBG (institution)); speakers' bureau from AstraZeneca, Daiichi Sankyo Europe GmbH, Novartis, Pfizer, Roche, Gilead Sciences, Seattle Genetics, Menarini Group, Agendia, Bayer, Medscape, MSD, Stemline Therapeutics, Streamedup! (paid to institution); research funding from Abbvie, AstraZeneca, Celgene, Novartis, Pfizer, Daiichi Sankyo, Gilead, MolecularHealth, Menarini Group, Greenwich LifeSciences (paid to institution); patents, royalties, other Intellectual Property: Patent Pending EP14153692.0, Patent Pending EP21152186.9, Patent Issued EP15702464.7, Patent Pending EP19808852.8, Digital Ki67 Evaluator, VM Scope GmbH (paid to institution). GBG Forschungs GmbH received funding for research grants from Abbvie, Amgen, AstraZeneca, BMS, Daiichi-Sankyo, Gilead, Molecular Health, Stemline Menarini, Celgene/BMS, Novartis, Pfizer and Roche (paid to the institution). GBG Forschungs GmbH has licensing fees from VMscope GmbH. In addition, GBG Forschungs GmbH has a patent EP21152186.9 pending, a patent EP19808852.8 pending, and a patent EP14153692.0 pending.

CD has patent VMscope digital pathology software, patent #WO2020109570A1, patent #WO2015114146A1, and patent #WO2010076322A1.

If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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