

Optimizing axillary lymph node management in early-stage HR+/HER2-breast cancer: Practical strategies for enhanced detection rates

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ABSTRACT

Introduction: Abemaciclib is a globally approved, standard-of-care adjuvant treatment for HR+/HER2-high-risk EBC which significantly improved outcomes in combination with ET, versus ET alone, in the pivotal monarchE trial. Nodal involvement is a major adverse prognostic factor in EBC; however, clarity around methods and timepoints for evaluation of involved ALNs and identification of high-risk patients eligible for adjuvant therapy is currently lacking.

Methods: A medical advisory board met virtually in November 2023 to discuss the changing landscape of axillary management in early breast cancer. The discussion assessed the knowledge gap caused by locoregional de-escalation for patients with HR+/HER- EBC leading to challenges in the appropriate identification of eligible patients for adjuvant CDK4/6 inhibitors. The panel aligned on recommendations to address these gaps and summarized these with the intent to raise awareness.

Results: Positive lymph node status can be denoted by pathological or clinical confirmation of breast cancer in ALNs. The panel therefore agreed that pragmatic strategies for ALN evaluation may include less invasive approaches such as ultrasound and clinical assessment. Evaluation of ALNs should be performed expeditiously post-diagnosis and before neoadjuvant treatment. A diagnostic algorithm has been developed to guide clinicians.

Conclusion: Optimized staging and risk assessment in HR+/HER2- EBC is critical to identify high-risk patients eligible for CDK4/6 inhibitors. Implementing these recommendations may improve patient outcomes in the adjuvant setting.

1. Introduction

Breast cancer is one of the most commonly diagnosed cancers

globally [1]. Early-stage breast cancer (EBC), defined as cancer localized to the breast or confined to the regional lymph nodes, constitutes roughly 90% of all cases [2]. Approximately 70% of these are of the

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hormone receptor positive (HR+), HER2 negative (HER2-) subtype [3]. Concurrent with a rise in BC cases [Bray 2024], survival rates have increased over recent years as a result of advancements in early detection and treatments [2] and continued work to elevate the standard of care [4].

To achieve optimal patient selection for breast cancer therapies, national and international treatment guidelines recommend the classification of patients into risk categories [2], which requires an accurate assessment of patients' staging at the outset [3]. Historically, treating the axilla was viewed as a curative therapeutic approach. However, studies have demonstrated that the role of axillary disease involvement is primarily prognostic, even in cases with positive sentinel lymph node biopsy (SLNB). Nevertheless, there are exceptions, such as in locoregionally advanced cases where local disease control is crucial [5,6]. Recent guidelines therefore advise that routine axillary lymph node dissection (ALND) is generally not recommended in patients with EBC with a negative or low burden of axillary disease [7,8]. Updated American Society of Clinical Oncology (ASCO) guidelines based on the INSEMA trial allow omission of SLNB for postmenopausal patients ≥ 50 years of age with negative findings on preoperative axillary ultrasound for grade 1-2, small (≤ 2 cm) HR + HER2- BC [9,10], despite new knowledge gaps (no partial breast radiotherapy allowed in INSEMA, overlapping indications for omission of SLNB and omission of radiotherapy).

The presence of nodal involvement, as assessed through clinical and pathological examination, stands out as a well-established adverse prognostic factor in all breast cancer subtypes, including early HR+, HER2- BC – as supported by numerous randomized clinical trials and meta-analyses [4,6,11]. Approximately 30% of patients with node-positive disease experience recurrence within the initial 5 years following treatment [12]. In HR + HER2-disease, even 5 years after cessation of endocrine therapy (ET), an increased risk of distant recurrence persists for at least 15 years, with risk strongly linked to the patients' original nodal status, tumor size, and histological grade [13,14]. In high-risk HR+, HER2- BC, the 10-year recurrence rate is reported as $\sim 40\%$ and the 10-year mortality rate as 30% [15]. The correlation between node positivity and a substantial tumor burden in the axilla with persistent risk of relapse in patients with HR+, HER2- EBC highlights the urgency for novel innovative therapeutic strategies [3].

The treatment options for HR+, HER2- EBC have significantly expanded leading to incremental improvements in clinical outcomes [4, 11,16]. However, clinicians face challenges in optimizing the selection and sequence of treatments in this complex landscape [17].

In the last 7 years, new targeted treatments in the form of CDK4/6 inhibitors (e.g. abemaciclib, palbociclib, ribociclib and dalpiciclib) have entered clinical practice, initially as treatments for advanced disease and, more recently, some are approved in EBC. Abemaciclib was the first CDK4/6 inhibitor with a license for use in the adjuvant setting in adult patients with HR+, HER2- EBC at high risk of recurrence [18,19]. Ribociclib is now also approved, in combination with an aromatase inhibitor, for the adjuvant treatment of HR+, HER2- EBC at high risk of recurrence [20]. Palbociclib is approved only in the advanced setting [21], following negative results in phase 3 trials (PENELOPE-B and PALLAS) in the EBC setting [22,23]. An additional CDK4/6 inhibitor, dalpiciclib, developed in China, is in phase 3 clinical trials for treating high-risk EBC and, in a pre-specified first interim analysis of the DAWNA-A trial, has shown very encouraging results in women with HR+/HER2- EBC and ipsilateral axillary lymph node involvement. Disease-free survival (DFS) was significantly higher with dalpiciclib plus ET versus placebo plus ET (hazard ratio [95% confidence interval] of 0.53 [0.42–0.67]; $p < 0.0001$) [24].

The pivotal phase 3 monarchE trial confirmed abemaciclib's effectiveness in reducing recurrence rates in high-risk patient cohorts receiving adjuvant ET, thereby establishing it as a standard component of care within this clinical setting [25]. Patients in monarchE were designated as high risk based on: ≥ 4 positive ALN or 1–3 positive ALN

and at least 1 of grade 3 disease, tumor size ≥ 5 cm or Ki67 $\geq 20\%$. Positive ALN required pathological or cytological confirmation of breast cancer in ALNs [26,27]. In this study, adjuvant abemaciclib plus ET demonstrated a persistent benefit in invasive DFS (IDFS) and distant relapse-free survival (DRFS) in patients with HR+, HER2-node-positive high-risk EBC ($n = 5637$). Five-year data also highlighted the sustained carry-over effect of abemaciclib, preventing one recurrence event (predominately incurable metastatic) for every 13 patients treated [28]. Hazard ratios for abemaciclib benefit were 0.680 and 0.675 for IDFS and DRFS, respectively, and 5-year absolute improvement in IDFS and DRFS rates were 7.6% and 6.7% [28]. Ongoing investigations into abemaciclib's impact on tumor size and proliferation markers suggest its potential utility in neoadjuvant therapy, contributing to tumor downstaging prior to surgical intervention [29,30]. A large translational program is also underway with abemaciclib, including work on the prognostic utility of circulating tumor DNA (ctDNA) in the monarchE trial [31,32].

Currently there is a need for a best-practice approach on detecting involved ALNs in HR+, HER- EBC, as this directly influences the determination of candidacy for adjuvant CDK4/6 inhibitor therapy. This manuscript reviews the available evidence and provides recommendations from an international panel of healthcare providers (HCPs), focusing on practical considerations to maximize lymph node detection rates.

2. Methods

Work on this project began in November 2023 when a panel of ten key HCPs specializing in breast cancer, in medical oncology, gynecology, surgery or pathology (two from Italy, two from Germany, two from Spain, and one each from Switzerland, Portugal, Austria and Brazil) convened virtually for a single advisory board meeting. The panelists received payment for their advice and input relating to data and topics presented by Lilly at the advisory board meeting. At the meeting, the HCP panel members presented the latest data disclosures for CDK4/6 inhibitors. Then, they discussed patient identification gaps for optimal treatment choices in HR+, HER2-, high-risk EBC, as well as existing guidelines for diagnostics on lymph node staging. The primary aim of the meeting was for the panelists to discuss and provide their opinions on issues relevant to the staging of ALNs and potential strategies to maximize the identification of high-risk patients eligible for adjuvant CDK4/6 inhibitor therapy. An additional aim was to add clarity on when (and how) lymph node status should be considered, before or after neoadjuvant therapy. In light of the acute clinical relevance of the discussed topics, following the advisory board meeting, the HCPs authored a manuscript aimed at increasing HCP understanding of the different approaches and trends in axilla management and their opinions on how best to integrate these into clinical practice. This manuscript was authored by the panel of HCPs and co-authored and funded by Lilly. Lilly also provided meeting minutes and discussed data/references from the advisory board with the panel members. The outcome of these discussions is provided in the form of a diagnostic algorithm. This best practice paper and associated diagnostic algorithm were developed within the framework of current European guidelines, with careful consideration given to the practical implementation of recommendations in real-world clinical settings.

3. Results

3.1. Current guidelines and consensus on ALN detection

Based on the panel's experience, guidelines from European Society of Medical Oncology (ESMO) and recently updated German Gynecological Oncology Group (AGO) are the most widely followed in current clinical practice in Europe and Brazil [8,33,34]. The St Gallen International Consensus Conference (SGBCC) also affords an important critical review

in the multidisciplinary team approach to EBC care and defines clinically important global standards of care [35]. Other guidelines are largely aligned with these leading the field [7,36–39]. Table 1 provides an overview of the current guideline recommendations on ALN detection in EBC. Table 2 outlines the types of axillary surgery that may be utilized in clinical practice for assessing node positivity and the associated definitions.

3.2. Current evidence on ALN detection and clinical context

Recent studies in the field of ALN detection, including studies directly comparing SLNB with ALND (Table 3), have afforded important evidence and insights with implications for clinical practice. However, studies omitting ALND that were conducted before the introduction of CDK4/6 inhibitors may be less clinically relevant in the current treatment landscape. Various clinical studies are also ongoing at this time that aim to demonstrate how ALND can be safely avoided in the post-neoadjuvant setting; publication of these results is anticipated to contribute further insight into this important area. Table 4 provides a narrative summary of findings from key studies in the field, together with panelist's opinions of their clinical significance and potential impact on ALN detection in real-world practice. It is important to note that the pivotal, but older trials, in this field did not employ contemporary surgical and radiotherapy techniques. Today, both ALND and RT planning are performed in a much more tailored way – thus the morbidity figures for all procedures cannot be applied to the contemporary clinical setting.

3.3. Clinical significance of optimized ALN detection

Despite clinical practice and guidelines moving towards de-escalation of axillary surgery, ALND remains necessary in certain subsets of patients and indications. These include those cases for which accurate axilla staging is critical and where lymph node status is required to direct systemic therapy. Acknowledging this, ESMO guidelines highlight the importance of multidisciplinary team discussion regarding the relevance of lymph node involvement in determining systemic therapy allocation, including the use of abemaciclib [8]. Adjuvant abemaciclib is recommended by the ESMO for patients with HR+, HER2-, node-positive EBC at high risk of recurrence with a Magnitude of Clinical Benefit Scale score of A3, and the National Comprehensive Cancer Network as a category 1 recommendation [7, 39]. Similarly, in the 2025 German AGO treatment recommendations, abemaciclib is rated with “AGO +”, indicating a high recommendation based on robust evidence [34].

Clinically accurate ALN assessment can therefore minimize the risk of under- or overtreatment, ensuring that patients receive the most appropriate interventions based on their disease characteristics. However, surgical decisions also need to consider the patient's well-being and the potential advantages of adjuvant treatment [3].

3.4. Panel recommendations

Opinions from the panel members drive efforts to optimize ALN detection and refine eligibility criteria for new therapies, influencing clinical practice and enhancing personalized care and outcomes for patients with breast cancer. Here, the panel highlighted the disparity between monarchE trial criteria and abemaciclib's licensed indication, emphasizing the importance of accurate lymph node assessment using various methods, as supported by studies such as AXSANA and SENOMAC [4,40]. They also acknowledged that, in cases where positive nodes are histologically identified and presumed characteristics of other nodes suggest positivity based on ultrasound findings, this is considered a confirmation of positivity.

Table 1
Current guidelines recommendations on ALN detection and diagnosis.

Guidelines group	Key recommendations
ESMO [8]	• SLNB is the standard staging approach for all clinically negative ALN patients (cN0) at diagnosis or after neoadjuvant chemotherapy due to reduced morbidity versus ALND [I, A] • In the absence of prior primary systemic therapy (PST), patients with micro metastatic spread and those with limited sentinel lymph node (SLN) involvement (1-2 affected SLNs) in cN0 do not need further axillary surgery. • ALND following positive SLNB with <3 involved SLNs is reserved for cases of expected high axillary disease burden or impact on further adjuvant systemic treatment decisions [II, A]. • While tumor micro or macro deposits in SLNs following PST should prompt ALND, isolated tumor cells (ITCs)^a do not appear to have an impact on local recurrence or the additional number of nodes involved. – If ITCs are detected, axillary and locoregional RT should be considered as an alternative to ALND if an impact on adjuvant systemic treatments is not anticipated.
AGO [33,34]	• Core needle biopsy (CNB) or fine needle aspiration (FNA) is advised to confirm axillary disease when ALNs appear suspicious either clinically or on ultrasound • If lymph node involvement is confirmed by biopsy in patients receiving adjuvant therapy, ALND is recommended. • For patients receiving neoadjuvant therapy, if lymph node involvement is confirmed by biopsy and they are candidates for targeted axillary dissection (TAD), a detectable marker should be placed in the metastatic lymph node to enable TAD in case of a clinical complete response in the axilla. • In the case of a clinical residual tumor in the lymph node, a new CNB should be considered as false positives can occur in approximately 30% of cases (AXSANA study). • TAD is recommended if not more than 3 suspicious lymph nodes are diagnosed prior to neoadjuvant chemotherapy. • Targeted lymph node excision (TLNE) without SLNB is not recommended and can be performed only in individual cases. • For patients with clinically negative ALNs, the standard procedure is SLNB.^b
St Gallen consensus (updated 2025) [35]	• Knowing a patient's nodal status, particularly in premenopausal women, is important based on the RxPONDER trial • The standard recommendation should remain as dissection and it is important to examine the size and biology of the tumor – The panel felt that, at present, it is too early to move just to nodal irradiation. – Patients with a positive node are likely to have a higher incidence of additional residual disease • Clinical factors can alter the risk of recurrence, with 4 positive lymph nodes considered a higher risk patient – In contrast to previous guidance, the panel's revised view was that number of lymph nodes <i>does</i> impact treatment, with 3 nodes set as the threshold for considering dissection

(continued on next page)

Table 1 (continued)

Guidelines group	Key recommendations
	- As the risk of recurrence increases, there should be more confidence in adding a CDK4/6 inhibitor - The panel noted a tendency to overestimate risk in the endocrine-sensitive population. For low biological risk, the prognosis is good and whether 2 or 3 years of CDK4/6i is required in this population should be carefully considered - The patient's actual risk of recurrence should determine the various treatment modalities (within the approved indication)
Other:	- Staging of breast cancer advised at initial diagnosis and post-surgery - SLNB recommended for clinically node-negative patients and ALND for those with positive SLNB results or suspicious nodes on imaging - Consistent criteria for axillary diagnosis: SLNB indicated for clinically node-negative patients (at time of breast surgery) and ALND for those with positive SLNB or suspicious nodes on preoperative ultrasound - Ultrasound use recommended preoperatively for all new diagnoses (NCCN and ASCO), or node-negative patients only (EUSOMA). - Emphasis on the role of imaging modalities, particularly MRI in high-risk patients (EUSOMA)
➢ European Society of Breast Cancer Specialists (EUSOMA) [36]	
➢ National Comprehensive Cancer Network (NCCN) [7]	
➢ American Society of Clinical Oncology (ASCO) [38]	

Abbreviations: ACOSOG, American College of Surgeons Oncology Group; ALND, axillary lymph node dissection; ALNs, axillary lymph nodes; ASCO, American Society of Clinical Oncology; AX, axillary; AXSANA, axillary surgery after neoadjuvant chemotherapy; cN0, clinically node-negative; CNB, core needle biopsy; EBC, early breast cancer; ESMO, European Society for Medical Oncology; EUSOMA, European Society of Breast Cancer Specialists; FNA, fine needle aspiration; ICARO, impact of chemotherapy on axillary response and outcomes; ITCs, isolated tumor cells; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PST, primary systemic therapy; RT, radiotherapy; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection; TLNE, targeted lymph node excision.

^a Therefore, in cases of ITCs and EBC with limited sentinel-node involvement, the evidence currently supports SLNB over ALND as supported by the retrospective ICARO trial (65).

^b In Brazil, although clinicians typically follow AGO guidelines, most surgeons will opt for SLNB with a dual tracer in the event of a negative axilla. Even if a single tracer is used, attempts will be made to find at least 3 nodes to diminish the false negative rate.

3.4.1. Abemaciclib efficacy

According to the panel, the monarchE trial's 5-year efficacy and safety data strongly support abemaciclib in addition to adjuvant ET as standard care for HR+, HER2-, node positive patients with high-risk EBC. In particular, they emphasized a 5-year absolute improvement in IDFS of approximately 8% attributed to adjuvant abemaciclib therapy and IDFS and DRFS rates of 7.6% and 6.7% [28]. These gains underscore the clinical importance and potential impact of accurate ALN detection on treatment outcomes.

3.4.2. Clarification of the abemaciclib European Medicines Agency label

In monarchE, patients were required to be node positive (microscopic and macroscopic tumor involvement allowed; ipsilateral internal mammary and supraclavicular lymph nodes allowed, but not counted toward the number of positive lymph nodes) and fulfill one of the following criteria (A) pathological tumor involvement in ≥4 ipsilateral ALNs OR (B) pathological tumor involvement in 1 to 3 ipsilateral ALN(s) (for patients who received neoadjuvant therapy also cytological tumor involvement at the time of initial diagnosis is allowed) and meet at least

Table 2
Concepts in axillary surgery [66].

Type of surgery	Description	Clinical setting	Purpose
Sentinel lymph node biopsy (SLNB)	• Identification and removal of the sentinel lymph node (s) marked by a (radioactive) tracer and/or blue dye, or SPIO or ICG, and suspicious lymph nodes determined by palpation	Upfront surgery After primary systemic therapy	Diagnostic
TARGETED APPROACHES (clip or seed marking of suspicious lymph node)			
Targeted lymph node biopsy (TLNB/MARI)	• Identification and removal of lymph nodes marked with a radioactive seed • MARI: marking ALNs with radioactive iodine seeds procedure	After primary systemic therapy	Diagnostic
Targeted axillary dissection (TAD)	• SNB + TLNB/MARI • Identification and removal of marked lymph nodes and SLNB • RISAS: radioactive iodine seed localization in the axilla with the sentinel node procedure, and targeted axillary dissection procedure	After primary systemic therapy After NACT and conversion from cN1CNB - > ycN0	Diagnostic
Targeted axillary surgery (TAS)	• TAD “plus” selective removal of “suspicious” nodes L1-3		Therapeutic in combination with radiotherapy
Axillary lymph node dissection (ALND)	• Resection according to anatomic boundaries of axillary lymphatic basins level I, II. • Optional to include level III	Upfront surgery After primary systemic therapy	Diagnostic and therapeutic

Abbreviations: ALN, Axillary Lymph Node; ALND, Axillary Lymph Node Dissection; ICG, indocyanin green; SLNB, Sentinel Lymph Node Biopsy; SPIO, super paramagnetic iron oxide; TAD, Targeted Axillary Dissection; TAS, Targeted Axillary Surgery; TLNB/MARI, Targeted Lymph Node Biopsy/Marking Axillary Lymph Nodes with Radioactive Iodine Seeds.

1 of the following criteria: grade 3 disease, tumor size of 5 cm or larger (cohort 1) or Ki-67 ≥ 20% [27].

In contrast, the European Medicines Agency (EMA) -approved abemaciclib label is less rigid than the monarchE study and defines positive lymph node status as either clinical or pathological confirmation of breast cancer in ALNs [19]. The FDA-approved indication for abemaciclib in EBC is similar to that of the EMA: clinical and pathological features consistent with a high risk of disease recurrence [41]. This broader EMA-approved definition may expand the pool of eligible patients for abemaciclib treatment, potentially offering more individuals access to this effective therapy. However, it also raises questions about the optimal selection of patients who would benefit most from adjuvant CDK4/6 inhibitors, as the criteria for positive lymph node status may vary between clinical trials and regulatory agencies.

3.4.3. Timing of axillary lymph node detection

The panel members agree that accurate analysis of axillary nodal status before neoadjuvant chemotherapy is crucial for assessing risk and determining CDK4/6 inhibitor eligibility. However, pathological confirmation of nodal positivity is not always necessary; a combination of core needle biopsy (CNB) of the primary tumor in the breast and

Table 3

Studies comparing SNB versus ALND; A: SNB versus axillary lymph node dissection (ALND), B: Experimental therapy.

A							
STUDY	PERIOD	MEAN AGE	F/U	INTERVENTION	SAMPLE SIZE (SNB/ ALND)	AXILLARY RECURRENCE (SNB/ALND)	OVERALL SURVIVAL (SNB/ALND)
Veronesi 2003 [67]	1998- 1999	Not available	3.8 years	SNB/ALND	259/257	0%/0%	99.2%/98.7%
Canavese 2009 [68]	1998- 2001	58 years	5.5 years	SNB/ALND	110/115	0%/0.9%	97.2% (both arms at 5 yrs)
ALMANAC [69]	1999- 2003	57 years	1 year	SNB/ALND	495/496	0.3%/0.8%	99%/99%
NSABP B32 [70]	1994- 2004	>50 years	7.9 years	SNB/ALND (SNB Negative)	1978/2011	0.4%/0.7%	91.8%/90.3%
B							
STUDY	RESIDUAL DISEASE (%)			LOCAL RECURRENCE (%)		EXPERIMENTAL THERAPY	
ACOSOG Z0011 [46]	27%			1.5% (10 years) SNB 0.5% (10 years) ALND		SNB	
IBCSG 23-01 [65]	13%			2.8% (5 years) SNB 2.4 % (5 years) ALND		SNB	
AATRM 048/13/2000 [71]	13%			2.5% (5 years) SNB 1.0 % (5 years) ALND		SNB	
AMAROS [6]	33%			1.82% (10 years) RT 0.93% (10 years) ALND		Radiotherapy	
OTOASOR [72]	38%			1.7% (8 years) RT 2.0% (8 years) ALND		SNB and Radiotherapy	
SINODAR [73]	44%			6.9% (5 years) ALND 2.1% (5 years) SNB		SNB	
SENOMAC [5]	34.5%			0.4 (3.9 years) SNB 0.5% (3.9 years) ALND		SNB	

Abbreviations: ALND, axillary lymph node dissection; BLS, breast-conserving surgery with sentinel lymph node biopsy; DISSECTION, axillary lymph node dissection; F/U, follow-up; NODAL RECURRENCE, recurrence in lymph nodes; SNB, sentinel lymph node biopsy.

radiological assessments of the ALNs may suffice. This approach grants clinicians more flexibility and latitude in assessing the number of involved lymph nodes, thereby aiding in determining patient eligibility for adjuvant therapy. It should be noted that in some countries CDK4/6 inhibitors are not approved or reimbursed. Hence, if there are access barriers to therapy, the panel agreed that the axilla treatment approach should remain unchanged.

3.4.4. Timing of abemaciclib therapy

ESMO, AGO, and SGBCC guidelines and recommendations are widely followed according to the panel members, but there is a need to clarify the initiation and timing of abemaciclib therapy. Failure to intensify treatment with CDK4/6 inhibitors in high-risk patients could lead to undertreatment of high-risk patients and eventually even to increased disease recurrence and negatively impact clinical outcomes. Patients can be considered candidates for abemaciclib based on lymph node status either at diagnosis or after surgery when the pathological nodal (pN) status is known. Confirmation of lymph node status, grading and size should therefore be established at the beginning of treatment, i. e., before neoadjuvant therapy.

To this end, early discussions and planning for the patient journey, including clinical and radiological lymph node assessment and potential adjuvant CDK4/6 inhibitor therapy, must be initiated as soon as possible upon diagnosis of HR+, HER2-, node positive, high-risk EBC, especially for patients undergoing neoadjuvant chemotherapy (NACT). Additionally, the treatment strategy, risk, and CDK4/6 inhibitor eligibility should be decided upon and aligned at this point, ideally as part of a multi-disciplinary team discussion. For patients slated to receive NACT, this means that accurate analysis of the axillary nodal status (quantifying the number of presumably positive nodes at presentation instead of stating only positive or negative) prior to preoperative therapy is necessary to assess clinical risk and to determine abemaciclib eligibility status. In addition to palpation and CT/MRI, ultrasound should always be part of the imaging assessment, with CNB if necessary. The histological grade and size/dimensions of the primary breast tumor also need to be well

documented at this stage. The panel members strongly recommended that patients referred from other centers be reassessed and/or re-examined as required to determine CDK4/6 inhibitor eligibility.

In addition, clinicians need to be aware that eligibility for adjuvant CDK 4/6 inhibitors must not be influenced by any subsequent response to NACT or adjuvant chemotherapy, and clinical high-risk features at diagnosis remain the most important factor for determining eligibility. However, it is important not to forget that some patients considered to be not eligible at presentation can still be candidates for treatment with upstaging in the final pathology result (i.e., more positive lymph nodes or larger tumor than initially assessed – if the stage was underestimated or the tumor has progressed upon NACT). The presence of nodal involvement at initial clinical staging remains a significant risk factor for relapse even among patients who achieve a pathological complete response (pCR) after neoadjuvant treatment [42]. Lymph node involvement after NACT (non-pCR) is prognostically more important than a non-pCR in the breast and may therefore be highly under-estimated, making it even more imperative to escalate the strategy and offer patients adjuvant treatment due to the presence of a residual tumor.

3.4.5. The role of imaging in ALN assessment

The panel members pointed out that healthcare practitioners can leverage their clinical expertise and rely on established standard practices in their respective countries to assess the number of involved lymph nodes and ascertain patient eligibility for adjuvant CDK4/6 inhibitor therapy. It is not mandatory to pathologically confirm positivity in all suspected ALNs in order to justify therapy escalation. The panel members advocate for a pragmatic strategy, suggesting a combination of CNB-proven positivity in one or two nodes with radiological assessments with ultrasound primarily. Clinical assessment for bulky axillary involvement by palpation is mandatory. Positron emission tomography-computed tomography (PET-CT) or magnetic resonance imaging (MRI) may yield additional information, but they are not routine techniques and insufficient for diagnosis alone. Ultrasound must therefore form part

Table 4

Recent evidence in the field of ALN detection: overview and clinical context.

Study	Key findings and clinical implications
SURGICAL	
ACOSOG Z0011 [46]	- These two randomized phase 3 trials evaluating the impact of ALND omission collectively argue in favor of less invasive axillary strategies in EBC. - ACOSOG Z0011 found no difference in 10-year OS outcomes with ALND versus no ALND in patients with T1-2 breast cancer, no palpable axillary adenopathy and 1-2 sentinel lymph node metastases. - In AMAROS, axillary radiotherapy offered comparable regional control to ALND (with significantly less morbidity) in patients with T1-2 primary breast cancer and no palpable lymph-adenopathy after a positive SLNB.
AMAROS [6]	- These trials may lead physicians to reconsider the necessity of ALND and opt for less invasive axillary strategies in selecting patients with breast cancer, potentially reducing morbidity associated with surgery. - Notably, both trials showed a high rate of lymph node metastases in the “non-sentinel-lymph nodes” (control) group, suggesting leaving a high proportion of sub-clinical lymph node metastases with no negative impact on long-term outcomes.
SENOMAC [5]	- This international trial compared complete ALND to no further axillary surgery in patients with clinically node-negative breast cancer (T1-T3) and 1-2 SLN macrometastases - Results showed that the omission of completion ALND was non-inferior to the more extensive surgery in these patients, most of whom received nodal radiation therapy. 5-year-recurrence free survival showed no significant difference between the ALND and the SLNB-only arm. - Using these data, physicians may weigh the benefits of omitting complete ALND in patients with clinically node-negative breast cancer with postoperative SLN metastases after both breast-conserving surgery (BCS) and mastectomy, prioritizing patient-reported outcomes and quality of life.
TAXIS [48]	- In this ongoing, global, multisite, phase-III study, patients are randomly assigned to tailored axillary surgery (TAS) followed by ALND and regional nodal irradiation, or TAS followed by regional nodal irradiation encompassing the entire axilla. - Findings could potentially prompt a reduction in the extent of axillary surgery for patients with clinically detected positive breast cancer nodes. - Future results from the TAXIS study and the various associated sub studies are likely to define TAS/TAD as an alternative to ALND in patients with clinically node-positive breast cancer and may lead to de-escalation of axillary surgery in this group.
INSEMA [9]	- This prospective, randomized, non-inferiority trial compared omission of axillary surgery versus SLNB in patients with clinically node-negative T1 or T2 invasive breast cancer. - According to primary results of the INSEMA trial, omission of surgical axillary staging proved non-inferior to SLNB after a median follow-up of 6 years. Estimated 5-year invasive DFS rates were virtually identical at 91.9% and 91.7%, respectively.
BOOG 2013–08 [74]	- This Dutch prospective, non-inferiority randomized multicenter trial is investigating whether SLNB can be safely omitted in patients with clinically node negative T1–2 invasive breast cancer undergoing breast-conserving therapy. - The primary outcome is 5-year regional recurrence rate with SNLB vs no SNLB (watchful waiting).
SOAPET [75]	This prospective phase 2 trial evaluated the feasibility of SLNB omission after integration of 18F-FDG dedicated lymph node PET in cN0 EBC

Table 4 (continued)

Study	Key findings and clinical implications
	- LymphPET was successfully used to identify cN0 patients, decreasing the false negative rate of clinical lymph node evaluation to <10% - The ongoing second stage of the SOAPET trial is assessing omission of SLNB according to pre-operational axillary evaluation integrating LymphPET.
NAUTILUS [76]	- This prospective multicenter RCT is investigating omission of axillary surgical treatment for lymph node-negative patients after ultrasonography. - Stage T1-2 and N0 patients receiving breast-conserving surgery will undergo axillary US (biopsy/aspiration of suspicious nodes is also allowed) and be randomized (1:1) into the no-SLNB (test) and SLNB (control) groups. - The primary endpoint is invasive DFS.
CALGB 9343 [77]	- This randomized trial compared the efficacy of tamoxifen alone (Tam) with tamoxifen plus adjuvant radiotherapy (TamRT) in older women (≥ 70 years) with ER-positive, EBC after breast-conserving surgery. - At 10 years, there was a small improvement in locoregional recurrence with TamRT vs Tam (98% and 90% of patients recurrence-free, respectively) but this did not translate into an advantage in OS, distant DFS or breast preservation.
SURGICAL POST-NEOADJUVANT	
SENTINA and Alliance Z1071 [78,79]	- These older studies showed that estimating the axillary nodal status of an initially node-positive patient after response to NST using SLNB alone and with the goal of avoiding ALND carries the risk of misestimating residual axillary tumor burden. - In both, removing 1 to 2 SLNs was associated with an unacceptable FNR of more than 10% - Results from studies such as SENTINA and Alliance Z1071 therefore suggest that SLNB alone might not be sufficient to assess axillary lymph node status after NST.
AXSANA [47,80]	- This ongoing, international, multicenter cohort study is evaluating different surgical methods of axillary staging in patients with clinically node-positive breast cancer treated with NACT, to determine whether de-escalation of axillary surgery is a safe option for patients converting from cN + to ycN0. - Findings may prompt physicians to consider de-escalating axillary surgery in patients undergoing neoadjuvant chemotherapy, balancing oncological outcomes with minimizing surgical morbidity. - Initial results from AXSANA analyzing the diagnostic performance of axillary US after NACT in initially node-positive BC patients have shown that the pathological nodal status cannot be reliably determined with US alone. - Sensitivity was 46.4%, specificity 78.8%, positive predictive value 64.2% and negative predictive value 64.3%.
ADARNAT [81]	- This Spanish multicenter, randomized, open-label, phase 3 trial will enroll 1660 patients with breast cancer and positive SLNs following NST. - It aims to assess whether axillary radiotherapy is non-inferior to ALND in terms of recurrence and overall survival in in this patient population, and if it can reduce surgery-related adverse effects. - Findings may help to confirm the efficacy and safety of an axillary radiotherapy approach over ALND in the post-neoadjuvant setting in patients with positive nodes.
SenTa (and early TAD studies) [50–52]	- Early studies have shown promising results with targeted axillary dissection (TAD) after NST where the target lymph node (TLN) is pre therapeutically marked - The German SenTa study of 548 node-positive patients (473 of whom received NST as well as a clip marking of the biopsied positive lymph node) confirmed the value of TAD in comparison to SLNB

(continued on next page)

Table 4 (continued)

Study	Key findings and clinical implications
	and TLNB alone; it represents the largest study on TAD to date.
	– TLNB was possible in 329/423 (77.8%) patients and a TAD was successfully carried out in 199/229 (86.9%). The TLN was in line with the SLN in 64.8%, while FNR for the TLNB was 7.2% and 4.3% for TAD.
SYSTEMIC THERAPY TRIALS	
monarchE [26–28]	• In this Phase 3 trial, patients with HR+, HER2– EBC at high-risk of recurrence (≥4 pathological positive nodes, or 1–3 nodes + either tumor size ≥5 cm, histologic grade 3, or central Ki-67 ≥ 20%) obtained significant benefit from abemaciclib plus ET – aromatase inhibitor or tamoxifen – compared with ET alone. • Two years of adjuvant abemaciclib plus ET led to a significant and sustained improvement in invasive DFS and distant relapse-free survival compared with ET alone. • The observed absolute benefit of abemaciclib plus ET for 2 years over ET alone persisted and increased at 5 years, consistent with a carryover effect—further supporting use of abemaciclib in patients with high-risk EBC.
NATALEE [82]	• Results from this Phase 3 trial, which evaluated adjuvant ribociclib in a broad population of patients with stage II or III HR+/HER2– EBC at risk for recurrence (including NO patients), indicate a benefit of CDK4/6 inhibition in patients without nodal involvement, as well those with node-positive disease. • Findings may therefore encourage physicians to consider CDK4/6 inhibition as an adjuvant therapy option for stage II and III patients with EBC with and without nodal involvement, potentially enhancing treatment efficacy. • A significant portion of these study participants (30%) were clinically node-negative, and 14% remained node-negative after treatment, underscoring the difference between initial clinical staging and staging after NACT. • Compared to NATALEE, the patients included in monarchE were a purely high-risk population.
DAWNA-A [24]	• This Phase 3 placebo-controlled trial evaluated dalpiciclib in combination with ET as adjuvant therapy for stage II or III HR+/HER2– EBC at high-risk for recurrence (pathologically confirmed ipsilateral axillary lymph node involvement). • Results of the pre-specified first interim analysis (median follow-up 20.3 months) were encouraging: DFS, invasive DFS and distant DFS were all significantly improved in the dalpiciclib group versus the placebo group.
OlympiA [83]	• This study evaluated PARP inhibition for patients with gBRCA1/2 pathogenic or likely pathogenic variants and high-risk clinicopathological factors who had received local treatment and neoadjuvant or adjuvant chemotherapy. – HR positive/HER 2 negative patients were required to have ≥4 pathologically confirmed positive lymph nodes • Findings indicate that, in case of BRCA1/2 mutation and an indication for abemaciclib, patients could be treated first with Olaparib and then sequentially with abemaciclib – As the monarchE protocol allowed patients to start with abemaciclib 16 months after local treatment (including surgery and radiation). • OlympiA findings could therefore influence physicians to incorporate PARP inhibition into treatment strategies for patients with breast cancer and high-risk features, including extensive lymph node involvement, in order to improve outcomes.
RxPONDER [84]	• This study used a 21-gene breast cancer assay and the extent of axillary disease to determine patient eligibility for omission of chemotherapy.

Table 4 (continued)

Study	Key findings and clinical implications
	• It found that premenopausal women with 1–3 positive lymph nodes and a recurrence score of 25 or lower experienced longer periods of invasive DFS and distant relapse-free survival when treated with chemoendocrine therapy compared to ET only – However, this conclusion is heavily contested, given the fact that only a small minority of these patients had optimal ET (i.e., ovarian function suppression). • Currently, there is intensive discussion on whether ovarian function suppression plays a more important role than chemotherapy in premenopausal patients. • Knowing this, physicians may opt to integrate gene assay data into treatment decision-making, allowing for more personalized management strategies and sparing certain patients from unnecessary chemotherapy.
ADAPT [85,86]	• This study aimed to establish early predictive surrogate response markers in order to individualize (neo)adjuvant decision-making in EBC. • It showed, in contrast to RxPONDER, that if pre- and postmenopausal patients responded to an ET induction of 3–4 weeks, with a Ki-67 drop of <10% and a recurrence score of <25, then chemotherapy was not beneficial – despite the presence of 1–3 positive lymph nodes. • Other ongoing trials in this area, such as OPTIMA, aim to refine and personalize adjuvant chemotherapy recommendations for patients with HR + EBC, potentially reducing overtreatment and improving outcomes for patients with breast cancer (https://www.optimabreaststudy.com/).

Abbreviations: ACOSOG, American College of Surgeons Oncology Group; ALND, axillary lymph node dissection; BCS, breast conserving surgery; CDK4/6, cyclin-dependent kinases 4 and 6; cN+, clinically node-positive; DFS, disease-free survival; EBC, early breast cancer; ET, endocrine therapy; FNR, false-negative rate; gBRCA1/2, germline BRCA1/2 mutation; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; NACT, neoadjuvant chemotherapy; NST, neoadjuvant systemic therapy; OS, overall survival; PARP, poly (ADP-ribose) polymerase; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; TAS, tailored axillary surgery; TAD, targeted axillary dissection; TLN, target lymph node; TLNB, targeted lymph node biopsy; ycN0, pathologically node-negative after neoadjuvant chemotherapy.

of the diagnostic approach as it is the best technique for examining the architecture of the lymph node (notably, the hilum-cortex ratio). Additional node positivity can be inferred and determined based on these reliable radiological and clinical criteria.

To distinguish between high versus low axillary nodal burden, ultrasound emerges as the preferred tool [43]. Trained and experienced operators can frequently estimate the number of potential positive lymph nodes using standardized ultrasound equipment and criteria with a sensitivity and specificity of ≥80% [44], thereby providing sufficient diagnostic certainty.

3.4.6. Diagnostic algorithm

The panel members developed a diagnostic algorithm (Fig. 1) for precise clinical assessment of ALNs, drawing from a blend of expert agreement and current guidelines. This schematic aims to furnish oncologists and surgeons with a pragmatic approach and clinical tool to assess patients’ lymph node status accurately and decide on adjuvant CDK4/6 inhibitor eligibility. The recommendation of the panel is that existing guideline algorithms may be strengthened by stipulating the need to document the number of positive ALNs at one of three defined time points: at initial presentation (before treatment), after NACT but before surgery (if NACT is indicated), and at the time of surgery.

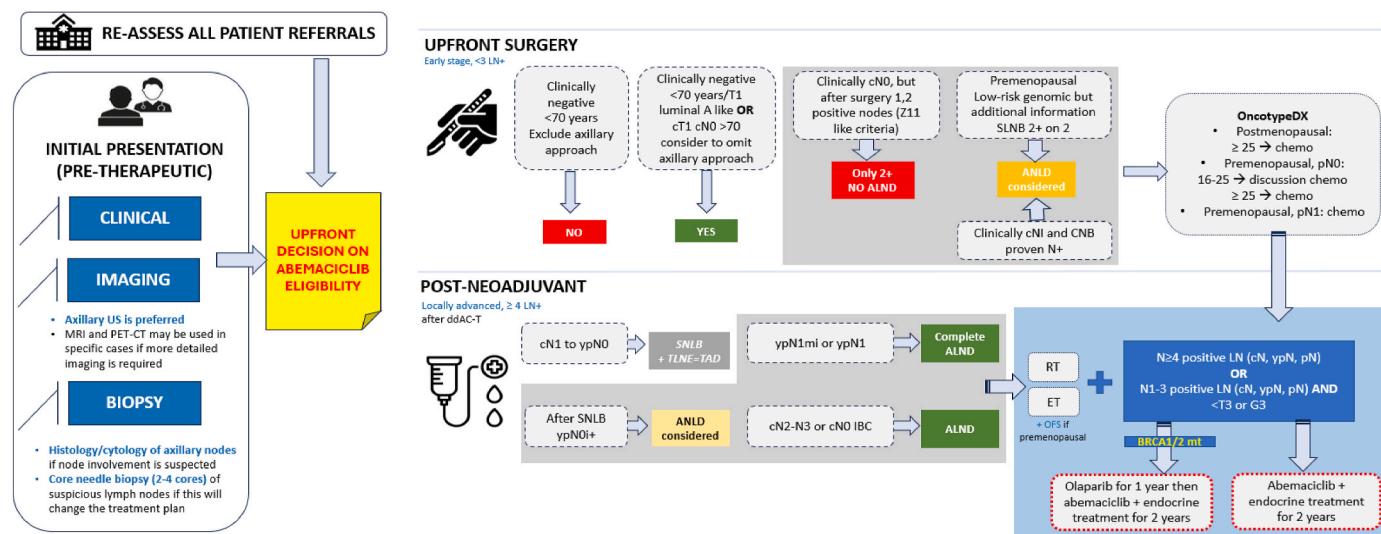


Fig. 1. Diagnostic algorithm: Axillary lymph node evaluation for abemaciclib eligibility in primary breast cancer.

4. Discussion

The assessment and staging of ALNs in EBC has evolved significantly in recent years, with guidelines now advocating for SLNB as the standard approach for clinically negative patients, either at diagnosis or post-neoadjuvant chemotherapy, due to reduced morbidity compared to ALND [8,33]. Consensus papers and recent trials, such as ACOSOG Z0011, AMAROS, SENOMAC also support less invasive axillary strategies even with 1-2 nodes positive at presentation [5,6,45,46]. Ongoing studies, for example, AXSANA and TAXIS, are exploring different approaches to evaluate the axilla after neo-adjuvant treatment [47,48]. With a focus on optimizing ALN detection and refining eligibility criteria for therapies such as abemaciclib, the panel members agree that the over-arching goal should be to enhance informed decision-making and tailor treatments to individual patients.

The panelists therefore advocate for SLNB as the standard for ALN detection in EBC due to its ability to accurately assess nodal status with less morbidity compared to ALND. SLNB instead of ALND is associated with a 65% lower risk of lymphedema, with no significant differences in the 5-, 8-, or 10-year overall survival (OS), DFS, or recurrence rates [45]. This approach aligns with the broader trend of surgical de-escalation in axillary management, aiming to balance thorough evaluation with minimally invasive techniques. The transition towards less invasive surgery, such as SLNB, is complemented by an increase in axillary radiotherapy, which is considered problematic by some of the panel members. This approach seeks to mitigate the risks of overtreatment and undertreatment, emphasizing the importance of precise nodal assessment. It should be noted that surgical techniques for approaching the breast and axilla are still important, and focus should be on nerve and lymphatic system protection, which are critical to minimize complications and improve patient outcomes [23,49].

In order to accurately assess both value and burden of modern axillary surgery, well-documented prospective clinical trials of targeted and contemporary axillary procedures are urgently needed, rather than premature conclusions arising from overstating theoretical extrapolations of essentially outdated locoregional treatment method comparisons [5]. For example, the pivotal but historic AMAROS trial does not reflect contemporary surgical techniques in the axilla, and thus markedly overstates surgical morbidity. Likewise, radiotherapy planning and techniques have greatly improved since then. It is highly unlikely that nowadays the retrieval of 4 or 5 more additional nodes will make a notable difference in morbidity for the selected number of patients where this information will translate into treatments that can benefit

survival.

Studies of targeted axillary dissection (TAD) have continued to demonstrate its important role in the de-escalation of surgical strategies and a move towards less invasive axillary staging for patients with breast cancer [50,51]. Most recently, the SenTa study, the largest conducted in TAD to date, confirmed the feasibility and accuracy of this approach in a real-world cohort of patients undergoing neoadjuvant systemic therapy [52]. Although targeted lymph node excision (TLNE) has a similar false-negative rate (FNR) to TAD, which includes both TLNE and SLNB, a recent systematic review confirms that it cannot yet be recommended to spare SLNB in the concept of TAD [53]. There are also issues around minimally invasive staging procedures such as SLNB or TAD which still need to be finessed, including the technical aspects of lymph node marking [54].

The number of isolated nodes in a contemporary ALND and the implications in comorbidities have not been studied in recent trials and the dogma of 10 nodes was valid for all the pivotal trials comparing axillary dissection with SLNB. However, the number of isolated lymph nodes in ALND was not associated with worse OS [55]. The panel members believe that in current clinical practice and excluding massively positive axillae, the information needed to offer patients a highly effective adjuvant treatment can be achieved at a lesser cost (6-7 isolated nodes) with a probably lesser impact on the arm. However, it is always important to consider the potential harm to patients where the presence of positive lymph nodes is missed, or the axillary burden underestimated, leading to a failure to intensify adjuvant treatment. Therefore, the development of alternative methods to define nodal status more comprehensively is crucial. Techniques such as ultrasound and MRI can offer detailed insights into nodal involvement, guiding adjuvant treatment decisions and potentially identifying candidates for therapies, for example, abemaciclib, as well as other therapies that depend on accurate axillary staging such as pembrolizumab and olaparib. Implementation of this broader and more clinical approach to defining nodal status has the scope to both improve patient stratification and treatment decision-making [3].

The effectiveness of US-guided CNB in detecting lymph node metastases in the axilla was confirmed in a recent systematic review and meta-analysis. Across 18 studies involving over 2500 patients with breast cancer, US-CNB demonstrated good overall specificity (0.99 overall) and sensitivity (0.90) in the preoperative diagnosis of ALNs [56]. Pre-operative US alone also showed predictive value in differentiating between low and high axillary tumor load, supporting its use as a tool to select the type of treatment [57]. In this prospective study of 142

patients, a highly statistically significant correlation (72.7%) and concordance (79%) between the number of positive lymph nodes on axillary ultrasound and the number of metastatic lymph nodes in the surgical specimen was established. For diagnosing high axillary tumor load (≥ 3 metastatic lymph nodes) versus low axillary tumor load (< 3 metastatic lymph nodes), axillary ultrasound demonstrated 86.6% sensitivity, 83.3% specificity, 92% positive predictive value, and 71.4% negative predictive value [57], highlighting its value as a diagnostic tool. The panel members acknowledge that practices for assessing and managing ALNs in EBC vary worldwide, reflecting differences in clinical guidelines, healthcare infrastructure and access to advanced diagnostic tools, in particular the implementation of ultrasound and staging with PET and CT.

While the long-term outcomes for patients with HR+/HER2-, high-risk, EBC have been improved with adjuvant CDK4/6 inhibitors, there also remain populations in whom treatment is more difficult [58]. Studies, including EPIGEICAM, show that comorbidities, such as obesity, and other patient-specific factors can negatively affect outcomes in breast cancer, suggesting the need for tailored treatment strategies for individual patient subgroups to improve prognosis [59–61]. Emerging evidence also highlights the importance of non-traditional biomarkers, such as PIK3CA, MAPK and retinoblastoma gene mutations, circulating tumor cells (CTCs), and ctDNA, in identifying high-risk patients who might benefit from newer, targeted treatments post-neoadjuvant chemotherapy [62–64]. Therefore, in addition to efforts to optimize ALN detection, it might also be reasonable to consider a deeper molecular evaluation in the setting of EBC to properly identify high-risk patients who will benefit from treatment with CDK 4/6 inhibitors.

5. Conclusion

The panel recommendations on the optimal approach to ALN detection for EBC underscore the critical importance of maximizing detection rates to identify high-risk patients eligible for adjuvant tailored therapy. This best-practice guidance is particularly significant in the context of evolving surgical de-escalation strategies in axillary management, where balancing the need for a thorough evaluation of the axilla with conservative surgical approaches is paramount.

The adoption of less invasive methods such as CNB, intensive imaging, and clinical assessments offers a pragmatic solution to accurately define nodal status and guide treatment decisions in cases where ALND is not warranted. A clinical diagnosis of positive lymph nodes is sufficient for evaluating eligibility for abemaciclib. It is therefore vital that ALNs evaluation and determination of nodal status, along with CDK4/6 inhibitor eligibility, occurs at the outset of the patient journey (ideally at diagnosis) and before the commencement of treatment. By implementing these recommendations, clinicians can enhance patient stratification and improve treatment outcomes in the adjuvant setting.

However, it is important to acknowledge the global variation in practice and consider additional factors influencing outcomes, such as diverse breast imaging expertise, obesity, and biomarkers of poor prognosis. Ultimately, accurate determination of ALN status remains pivotal in optimizing overall breast cancer survival outcomes and ensuring eligible high-risk patients with HR+, HER2- EBC receive appropriate therapy and enhanced care.

CRedit authorship contribution statement

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Abbreviations

AGO	German Gynecological Oncology Group
ALN	axillary lymph node
ALND	axillary lymph node dissection
CNB	core needle biopsy
CT	computed tomography
ctDNA	circulating tumor DNA
DFS	disease-free survival
DRFS	distant relapse-free survival
EBC	early breast cancer
EMA	European Medicines Agency
ESMO	European Society of Medical Oncology
ET	endocrine therapy
HCP	healthcare providers
HER2	human epidermal growth factor receptor 2 negative
HR+	hormone receptor positive
IDFS	invasive disease-free survival
MRI	magnetic resonance imaging
NACT	neoadjuvant chemotherapy
OS	overall survival
pCR	pathological complete response
SGBC	St. Gallen International Consensus Conference
SNLB	sentinel lymph node biopsy
TAD	targeted axillary dissection
TLNE	targeted lymph node excision
US	ultrasound

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