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Tumour Review

De-escalation strategies for axillary management at primary surgery in early breast cancer: insights and implications for medical oncology practice

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ABSTRACT

The recognition that axillary surgery in early breast cancer primarily serves as a staging tool rather than a curative treatment, along with the shift from axillary lymph node dissection (ALND) to sentinel lymph node biopsy (SLNB) as the standard procedure for clinically node-negative patients, has paved the way for further de-escalation of axillary treatment. This strategy aims to reduce treatment-related morbidity while preserving survival outcomes. Multiple studies have provided compelling evidence that ALND can be safely omitted in cases of limited SLN involvement. Moreover, even the omission of SLNB in selected low-risk cohorts has been shown not to increase recurrence rates. On the other side, from the oncological perspective, research has moved toward an escalation of adjuvant treatments, aiming to reduce recurrence rates and improve overall survival. Thus, while residual axillary disease does not affect patient outcomes, limited axillary staging may hinder access to certain adjuvant therapies. Here, we aim to critically assess the potential impact of recent advances in axillary surgical de-escalation on adjuvant systemic therapy decision-making especially in hormone receptor positive/HER2 negative early breast cancer, with a particular focus on the appropriate selection of patients for adjuvant chemotherapy, CDK4/6 inhibitors, and PARP inhibitors. We argue that decisions on surgical de-escalation should be carefully tailored, balancing its potential benefits with the need for accurate staging to guide adjuvant therapies. A patient-centered, multidisciplinary approach remains essential to ensure that de-escalation does not impact negatively on adjuvant treatment decision making and long-term survival.

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Background

Breast cancer (BC) is the most frequent cancer worldwide and the leading cause of cancer death in women. While the global incidence has risen over time due to earlier detection, the mortality has significantly reduced thanks to advances in treatment, particularly in high-income countries [1]. Most BC cases are diagnosed at early stage (EBC) and treated with multimodal treatment strategies, tailored to the disease stage and biology. Axillary nodal status is an established key prognostic factor in BC, playing a crucial role in informing decisions regarding surgery, radiotherapy (RT), and systemic therapy [2]. Axillary-lymph-node dissection (ALND) has long been considered the standard treatment for axillary staging. However, the rate of surgical complications associated with ALND is substantial, affecting up to 70% of patients in the form of wound infections, seroma formation, paresthesia, and lymphedema [3]. This aspect is particularly relevant in the current era, where improved survival rates among BC patients have brought increased attention to survivorship and quality of life (QoL). Since the early 2000s, the introduction of sentinel lymph node biopsy (SLNB) has enabled a more conservative surgical approach without compromising survival outcomes, thereby laying the foundation for subsequent de-escalation strategies in axillary surgery [4]. Supported by evidence from multiple non-inferiority trials, current guidelines and international expert consensus have progressively endorsed axillary surgery de-escalation as a recommended approach for primary locoregional management in EBC. SLNB remains the standard method for axillary staging in patients with clinically negative axillary lymph nodes (ALNs). By contrast, the indications for ALND are progressively being restricted. While ALND continues to be recommended in cases with clinically positive ALNs, guidelines now support omitting ALND in patients with small (T1–T2), clinically node-negative (cN0) tumors and 1–2 positive SLNs, when post-operative radiotherapy and appropriate adjuvant systemic therapy are administered [5–8]. More recently, three studies have further advanced this perspective, suggesting not only that axillary surgery does not confer a therapeutic benefit itself, but also that imaging alone may provide reliable staging of ALNs, potentially obviating the need for SLNB [9–11]. Furthermore, an increasingly refined understanding of tumor biology has shifted the focus from loco-regional disease control to the management of "occult" disease, both locally and at distant sites, through therapies that are progressively tailored to the individual's clinical and biological risk profile. In this context, a "radical surgical sparing approach" may help reduce long-term morbidity in potentially cured patients, but it also raises concerns about its impact on oncological practice. Notably, recent clinical trials have highlighted significant improvements in long-term outcomes through the intensification of adjuvant therapy for patients with high-risk features, including ALNs involvement. Omitting axillary surgery carries the risk of missing patients who could benefit from these therapies. Here, we aim to provide an in-depth analysis on the implications for medical oncology practice of the most recent practice-changing studies on upfront axillary surgery in EBC.

Potential therapeutic implication of ALND omission

Data supporting omission of axillary dissection in positive sentinel nodes

The necessity of ALND in patients with cN0 EBC who have one to two positive SLNs has long been a subject of debate. Previous trials such as ACOSOG Z0011[12], AMAROS [13], OTOASOR [14], SINODAR-ONE [15] demonstrated that, in selected patients, omitting ALND did not increase the risk of recurrence or mortality. While these studies have established the safety and efficacy of this approach, some variability in interventions, limited representation of high-risk subgroups, and certain statistical considerations may affect the broad applicability of these findings. To address these gaps, the prospective, randomized SENOMAC trial was conducted in Europe enrolling over 2,000 patients (Table 1) [16]. Eligible participants had a confirmed cN0 status at diagnosis, established via clinical examination and mandatory axillary ultrasound (AUS), and one to two macrometastatic SLNs after surgery. Compared to earlier trials, the SENOMAC cohort exhibited higher-risk features: over

Table 1
Comparison of inclusion criteria, design and outcomes between the main studies evaluating axillary dissection omission strategies.

		ACOSOG Z0011	AMAROS	OTOASOR	SINODAR-ONE	SENOMAC
STUDY DESIGN		ALND* vs. no further surgery after SLNB	ALND* vs. ART	ALND* vs. RNI	ALND* vs. no further surgery after SLNB	ALND* vs. no further surgery after SLNB
N. OF PATIENTS (PP)		813	1133	474	822	2540
INCLUSION CRITERIA	**Clinical tumor stage**	cT1–T2, N0	cT1–T2, N0	cT ≤ 3 cm, N0	cT1–T2, N0	cT1–T3, N0
	Pathological tumor stage	pN1a (1–2 SLNs with macro and micrometastases)	pN1a-pN1mi	pN1a-pN1mi	pN1a (1–2 positive SLNs)	pN1a (1–2 SLNs with macrometastases)
	Extracapsular extension	Excluded	NA	NA	NA	Included
	Surgery type	Upfront BCS	Upfront BCS/MT	Upfront BCS/MT	Upfront BCS/MT	Upfront BCS/MT
	Type of adjuvant radiotherapy	WBI (RNI not allowed**)	WBI/chest wall/ Internal mammary chain RT	WBI/chest wall RT	WBI (ART not allowed)	WBI/chest wall RT +/- RNI
PRIMARY ENDPOINT (ALND vs experimental arm)		OS*** (10y-OS: 86.3 % vs 83.6 % in the SLNB and ALND group, respectively (HR, 0.85 [1-sided 95 %CI, 01.16]; noninferiority P = 0.02)	5y-ARR*** (0.43 % vs 1.19 %, one-sided 95 % CI for the underpowered non-inferiority test on the HR 0.00–5.27)	ARR (2.0 % vs. 1.7 %, P 1.00)	OS (5-yOS: 98.9 % vs 98.8 %,P 0.936) ***	OS (5y-OS: 92.9 % vs 92.0 %)****
MEDIAN FOLLOW-UP (m)		112	120	97	34	46.8

PP: per-protocol population; ALND: axillary lymph nodes dissection; SLNB: sentinel lymph node biopsy; MT: mastectomy; WBI: whole breast irradiation; ART: axillary radiotherapy; RNI: regional nodal irradiation; RT: radiotherapy; BCS: breast conservative surgery; MT: mastectomy; ARR: axillary recurrence rate; NGL: national guidelines; LRR: locoregional recurrence rate.
*Dissection of at least anatomical levels I and II including at least ten nodes.
**RT records revealed that 19% of patients received RT to the supraclavicular fossa contrary to protocol-specified treatment.
*** Statistical power not reached for the primary endpoint.
**** Statistical power has not yet been obtained for this endpoint.

35 % underwent mastectomy, nearly 50 % had large tumors (pT2 or pT3), and a considerable fraction displayed grade 3 histology (22 %) and high proliferation index (mean ki67 24–25 %). Patients were randomly assigned to either SLNB only or ALND. While data on the primary endpoint (overall survival, OS) are not yet mature, the estimated 5-year recurrence-free survival (RFS) was 89.7 % (95 % CI, 87.5 to 91.9) in the SLNB–only group and 88.7 % in the ALND group, with an HR of 0.89 (95 % CI, 0.66 to 1.19) which was significantly below the noninferiority margin. Notably, locoregional and distant recurrence rates were not increased in the SLNB-only arm, despite the fact that 34.5 % of patients in the ALND group had additional positive ALNs removed, with an even higher rate (51.3 %) in patients with initial two positive SLNs. Moreover, among patients with positive non-sentinel nodes, 9.9 % were ultimately upstaged to pN2 (4–9 positive nodes) and 3.0 % to pN3 (≥10 positive nodes). Therefore, it is conceivable that some patients in the axillary surgery-sparing arm might be excluded from intensified adjuvant therapies, despite harboring clinically high-risk disease. Although ALNs generally reflect the genomic landscape of the primary breast tumor, the clinical outcomes associated with residual disease in the breast versus the axilla differ substantially [17]. Positive surgical margins in the breast are associated with a markedly higher risk of recurrence, approaching 28 % at five years in patients with greater than focally positive margins, whereas residual axillary disease seem to carry a much lower risk [18].

This discrepancy is not yet fully understood, but it may be partly explained by established differences in the tumor microenvironment between primary tumors and ALNs [19]. Moreover, preclinical data indicate that distant metastases are primarily driven by hematogenous spread from the primary tumor, while axillary involvement appears to be a secondary and less effective route, possibly underlying the low incidence of distant relapse [20].

By demonstrating reductions in postoperative complications, mostly lymphedema and arm dysfunction, the results of SENOMAC trial contributed to support a shift toward more conservative axillary treatment strategies in EBC [21]. Nonetheless, some concerns persist. First, the current duration of follow-up may still be insufficient to fully capture long-term outcomes of patients with luminal tumor subtype, which is known for its tendency toward late recurrence. Secondly, the trial did not adequately address the appropriateness of post-operative RT when ALND is omitted, as it did not report details on target volumes or doses to specific nodal levels. Notably, nearly all patients managed with SLNB alone received regional nodal irradiation in accordance with Northern European guidelines, thereby making it difficult to distinguish the effect of omitting ALND from the therapeutic impact of local irradiation. Another practical issue not addressed by the trial is the optimal management of patients in whom all retrieved SLNs are finally positive (e.g. 1/1 or 2/2). A recent real-world analysis of current practice patterns in this setting showed that clinicians indicated ALND in 41 % of patients with 2/2 positive SLNs and in 26 % with 1/1, with additional axillary disease identified in over 50 % and 40 % of these groups, respectively [22]. The information gained from ALND appeared to influence systemic treatment, with more postmenopausal patients receiving adjuvant chemotherapy even though they remained pN1 and had similar 21-gene recurrence scores. Notably, though limited by the retrospective design and the short follow-up, the study reported comparable OS rates between SLNB and ALND groups.

Overall, these findings highlight the need for multidisciplinary discussion in this “grey area”: while ALND may expose most patients to surgical morbidity and potential overtreatment, it may still be beneficial in selected cases, particularly those with 2/2 positive SLNs or in presence of predictors of additional nodal involvement, such as lymphovascular invasion and larger tumor size [23].

Adjuvant abemaciclib: is this still an issue?

An important and timely concern is whether limited axillary staging could unintentionally exclude patients who may benefit from intensified adjuvant systemic therapy. This is particularly relevant for high-risk patients, such as those meeting the criteria of the monarchE trial, which showed that the addition of abemaciclib to adjuvant endocrine (ET) therapy significantly reduces the risk of recurrence and death [24]. Based on data from the SENOMAC trial, nearly 13 % of patients with 1–2 positive SLNs who were ultimately found to have a final pN2 or pN3 nodal status might be excluded from receiving abemaciclib, despite they could have benefited from this effective treatment. The updated ASCO guidelines acknowledge this concern, suggesting that ALND can be considered in cases where patients with 1–2 positive SLNs are otherwise ineligible for abemaciclib based on tumor characteristics [25].

However, given the substantial morbidity associated with ALND, a critical consideration is whether it is worthy to perform an invasive and potentially harmful procedure just to potentially candidate a patient to abemaciclib. Indeed, the high-risk population in the monarchE trial included patients with 1–3 positive LNs if the tumor was grade 3 or ≥ 5 cm in size, as well as patients with ≥ 4 positive lymph nodes, regardless of tumor characteristics. This issue was specifically explored in a post-hoc analysis of the SENOMAC trial, which assessed the clinical implications of omitting ALND in patients whose eligibility for adjuvant abemaciclib would be based solely on meeting the pN2–3 criterion. The analysis introduced a composite approach that integrated the number needed to diagnose (i.e., the number of patients who would need to undergo completion ALND to identify one additional candidate for abemaciclib according to the monarchE inclusion criteria), with the absolute risk reduction in 5-years invasive disease-free survival (5y-iDFS) observed with abemaciclib versus placebo. By extrapolating these data, the authors estimated that 104 patients would need to undergo ALND to prevent a single iDFS event at 5 years, of whom 9 will develop severe or very severe impairment of physical arm function one year after surgery. On this basis, the authors concluded that performing ALND primarily to uncover potential eligibility for abemaciclib carries a disproportionate risk of treatment-related morbidity relative to the modest clinical benefit and therefore should not be recommended for this purpose [26].

Furthermore, the concern regarding the exclusion of patients from abemaciclib may be mitigated by the fact that the same patients who meet the eligibility criteria of the SENOMAC trial would still be eligible for treatment with ribociclib.

Adjuvant Ribociclib: can the surgical staging of the axilla influence treatment eligibility?

Patients with stage II disease were largely excluded from the monarchE trial, except when 1–3 positive ALNs and additional adverse biologic characteristics were present. The NATALEE trial is a phase III randomized study evaluating ribociclib plus ET versus ET alone in a broad population of patients with HR+/HER2 − EBC, including patients without nodal involvement in presence of biological features associated to poor prognosis (grade 3, grade 2 with Ki67 ≥ 20 %, or high genomic risk) or large tumor size (≥ 5 cm) [27].

By demonstrating a significant and sustained improvement in both iDFS and distant disease-free survival (DDFS), with a positive trend in OS, adjuvant ribociclib obtained approval from the United States Food and Drug Administration (FDA), and the European Medicines Agency (EMA). In the NATALEE trial, around 84 % of patients had node-positive disease, with approximately 41 % classified as pN1, a subgroup that could be eligible for ALND. Remarkably, though specific data on the N1 cohort are still not available, patients with node positive disease (N1-3) enrolled in NATALEE represents a high-risk population, as suggested by the substantial recurrence risk (5y-IDFS 80.5 %) and the high proportion of patients who received neoadjuvant or adjuvant chemotherapy (88 %) [28,29].

According to a large retrospective analysis on United States Electronic Health Records database, when applying the eligibility criteria for

both NATALEE and monarchE trials in a real-world population it appears that 30.6 % of patients with HR+/HER2- EBC meet the eligibility criteria for adjuvant ribociclib versus 14.5 % for abemaciclib. This difference is primarily driven by the subgroup of patients with pN1 disease, which accounts for nearly 20 % of the overall population [30]. In this context, identifying which patients eligible for adjuvant ribociclib truly derive a meaningful clinical benefit it is crucial. To better understand how accurate surgical staging of the axilla may (or may not) influence subsequent treatment decisions, we considered several representative clinical scenarios and explored the therapeutic approach we would recommend in each case.

In the common scenario of a patient with HR+/HER2 − EBC who meets the criteria for omission of ALND, systemic treatment strategies may still differ based on biological features, genomic risk, and the extent of nodal involvement. For patients with grade 3 tumors, ALND can generally be omitted, as these patients already meet criteria for adjuvant abemaciclib (Fig. 1, A). However, in patients with grade 1 or 2 tumors, additional prognostic factors, such as progesterone receptor (PgR) expression and Ki67 proliferation index, may help further stratify recurrence risk and guide adjuvant treatment decisions (Fig. 1, B). To achieve more accurate risk stratification of this subgroup and prevent unnecessary treatment escalation after standard chemo-endocrine

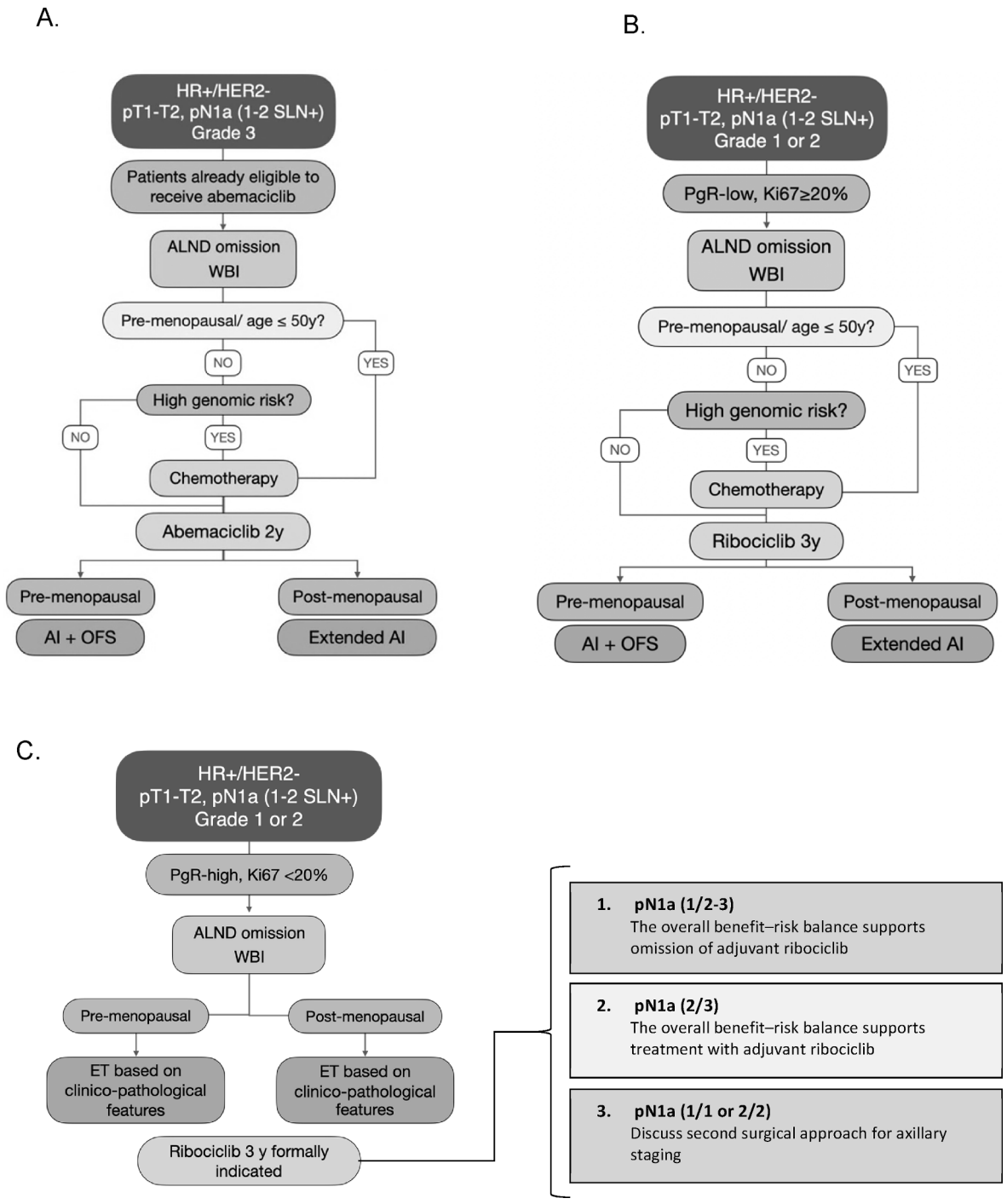

Fig. 1. Proposed possible treatment algorithm for patients with HR+/HER2- EBC who meet the criteria for ALND omission as per SENOMAC trial with grade 3 tumor (A), grade 1–2 tumor with high-risk biological features (B), with grade 1–2 tumor with low-risk biological features (C). SLN: Sentinel Lymph Node; WBI: whole breast irradiation; ALND: Axillary-Lymph-Node Dissection; SLNs: Sentinel Lymph Nodes; PgR: Progesteron Receptor; ET: Endocrine Therapy; y: years.

therapy, a recent international study has shown that computational analysis of routinely collected clinicopathologic data and tissue specimens can produce robust prognostic scores potentially implementable in clinical practice [31]. Conversely, patients with favorable features such as high PgR and low Ki67 may represent a lower-risk group where both surgical and systemic treatment de-escalation might be appropriate. In these situations, the degree of nodal involvement may still provide useful information. Data from the SENOMAC trial suggest that patients with a single macrometastatic SLN have a 31.3 % likelihood of harboring additional positive non-sentinel nodes. When this limited axillary burden is combined with favorable tumor biology, it may support omission of both ALND and ribociclib, despite formal eligibility for the latter. However, if two sentinel lymph nodes are involved, the probability of further nodal disease increases to over 50 %. In this case, omitting ALND may still be reasonable, but the addition of ribociclib to ET could be considered. In patients with involvement of all sampled sentinel nodes (1/1 or 2/2), more accurate axillary staging may still be warranted to guide optimal treatment planning, as previously discussed (Fig. 1, C).

The issue of Olaparib in the adjuvant setting

A possible exception to the omission of axillary dissection in patients who meet the eligibility criteria for the SENOMAC trial may be patients with luminal EBC carrying a germline pathogenetic BRCA1/2 mutation (gBRCA PVs). Compared to wild-type patients, patients with luminal EBC and gBRCA PVs have higher OncotypeDx recurrence score (RS), suggesting an intrinsically less favorable biology [32]. In the OlympiA phase III trial, the HR + subgroup that underwent upfront surgery was required to have at least 4 pathologically confirmed positive ALNs [33]. In this population, a considerable risk of recurrence was observed, with 22.8 % of patients in the placebo arm developing invasive disease or dying within 3 years. Adjuvant olaparib provided a significant improvement in IDFS and DDFS, that translated into a statistically significant OS benefit (6-year OS: 87.5 % vs 83.2 %), in both HR-negative and HR + patients [34].

Based on these results, olaparib was approved by international health authorities in 2022 for adjuvant treatment in patients with HER2-negative EBC and gBRCA1/2 PVs. Given these considerations, omitting ALND according to the SENOMAC criteria raises concerns about potentially excluding approximately 13 % of patients from receiving adjuvant olaparib (Fig. 2). The 2025 ASCO guidelines update addressed this issue, stating that ALND following a positive SLNB is not required if the patient is already eligible for olaparib. Otherwise, completion ALND may be considered by weighing the relatively low likelihood of axillary upstaging (13 %) against the significantly greater morbidity associated with ALND compared to SLNB [25].

Potential therapeutic implication of SLNB omission

Data supporting omission of sentinel lymph node biopsy

Three prospective noninferiority phase III studies addressed the issue of whether SLNB can be safely omitted in select patients with a negative finding on preoperative axillary ultrasound (AUS): The Sentinel Node versus Observation After Axillary Ultra-Sound (SOUND) trial, the Intergroup-Sentinel-Mamma (INSEMA) trial, and the BOOG 2013–08 [9–11].

The SOUND trial randomized 1,405 women undergoing upfront surgery for small tumors (up to 2 cm) to SLNB versus no SLNB after a negative preoperative axillary US. The primary endpoint, 5-y DDFS, was similar between the two groups (97.7 % in the SLNB group and 98.0 % in the no-surgery group, HR 0.84; P for noninferiority = 0.02). This trial enrolled patients with low-risk characteristics: most patients had a stage I disease with a median tumor size of 1.1 cm, HR+/HER2- was the most represented subtype (87.8 %), and patients with doubtful or suspicious lymph nodes, bilateral breast cancer, extensive multifocality or multicentricity were excluded. On the other hand, a substantial proportion of patients with high-risk biological features were included: more than 35 % patients had a high-proliferative disease (Ki67 ≥ 20 %), PgR was unexpressed in around 15 % of cases and almost 20 % of patients had a grade 3 tumor.

In the standard-care cohort undergoing SLNB, axillary upstaging after a negative AUS occurred in 13.7 %. Most of these cases involved a

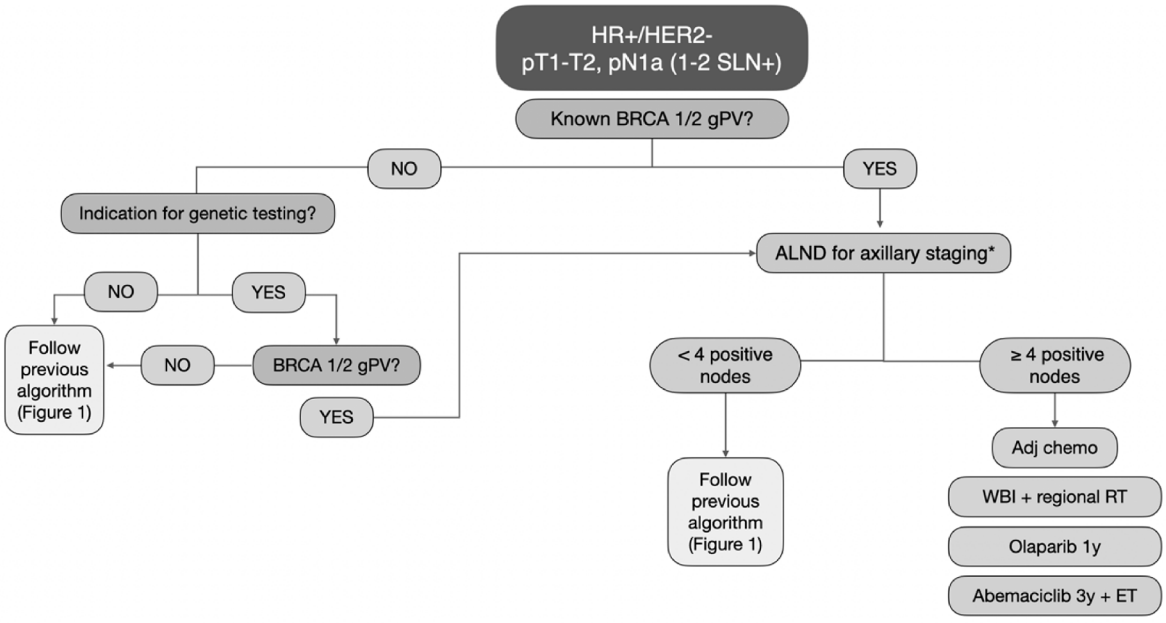

Fig. 2. Possible treatment algorithm for patients with HR+/HER2- EBC who meet the criteria for ALND omission as per SENOMAC trial and carry a germline pathogenic or likely pathogenic variants in BRCA1 or BRCA2. gPV: germline pathological variant; SLN: Sentinel Lymph Nodes; ALND: Axillary-Lymph-Node Dissection; ET: Endocrine Therapy; WBI: Whole Breast Irradiation; RT: Radiotherapy; y: year. * In the SENOMAC trial, ≥3 sentinel lymph nodes were removed in nearly 30 % of patients in both arms (median, 2 SLNs). In real-world practice, the number of excised SLNs may vary and when the ratio of positive SLNs to total SLNs removed is low, the clinical benefit of ALND may be limited and its indication should be individualized and discussed.

single additional positive SLN (11.7 %), and only 8.6 % had macrometastatic disease.

The INSEMA trial randomized 5,502 patients eligible for BCS across Germany and Austria in a 1:4 ratio to either no axillary surgery or SLNB. The primary endpoint 5y-iDFS was 91.9 % in the no-surgery group and 91.7 % in the SLNB group (HR, 0.91; 95 % CI, 0.73–1.14), meeting the prespecified margin for noninferiority. Moreover, omission of SLNB resulted in lower rates of morbidity and improved QoL.

Despite including a broader population, comprising also patients with cT2 tumors, the per-protocol population showed lower-risk biological characteristics as compared to SOUND trial. Particularly, 3.6 % of patients had grade 3 EBC, 12–13 % of patients had a high-proliferative tumor (Ki67 $\geq$ 20 %), and 95.2 % of tumors were luminal subtype. The number of patients with nodal metastases among patients randomly assigned to the SLNB arm was 15.1 %, with 11.6 % with sentinel macrometastases. Notably, patients with larger tumors (cT2) had a significantly higher risk of upstaging of the axilla to pN1a (20.8 %).

More recently, the preliminary results of the Dutch BOOG 2013–08 study have been reported. Consistent with the previously discussed studies, the BOOG 2013–08 randomized 1,572 patients with invasive unilateral cT1-2 BC, cN0 status confirmed by AUS, and planned to receive BCS to SLNB versus no SLNB. Of note, in this trial neoadjuvant systemic treatment was not an exclusion criterion. At a median follow-up of 5 years, regional recurrence-free survival (RRFS) was 96.6 % in the SLNB arm and 94.2 % in the no-SLNB arm, corresponding to an absolute difference of 2.35 % (95 % CI, 0.06–4.72), which did not exceed the prespecified 5 % noninferiority margin. Additionally, an absolute difference of 3.3 % in DDFS was observed between the two groups.

Among patients undergoing SLNB, macrometastatic involvement of the SLN was observed in 7.7 % of cases, while micrometastatic disease was identified in 6 %. However, these rates should be interpreted cautiously, given the possible impact of including patients treated with neoadjuvant therapy. Based on these results, the 2025 ASCO guidelines recommend that SLNB should be omitted for selected patients with negative findings on preoperative AUS who are postmenopausal and $\geq$ 50 years of age, with unifocal, grade 1–2, HR+/HER2- invasive ductal carcinoma $\leq$ 2 cm, for whom adjuvant ET is planned [25].

Similarly, the 2025 St. Gallen panel advised that SLNB surgery may be safely omitted in postmenopausal women with stage I, HR+/HER2- BC of grade 1–2, while voting against (60 % versus 40 %) the omission for lobular breast cancer due to the limited sensitivity of AUS in this setting [8].

By contrast, the current AGO (Arbeitsgemeinschaft Gynäkologische Onkologie) guidelines recommending the omission of SLNB do not distinguish between invasive ductal carcinoma and invasive lobular carcinoma [35]. Evidence supporting this unified approach comes from the subgroup analysis of the INSEMA trial, which included more than 600 patients with lobular or mixed ductal–lobular histology. The forest plot analysis demonstrated no differential effect by histologic subtype, thereby reinforcing the applicability of SLNB omission criteria to both ductal and lobular tumors within the trial's eligibility framework.

Beyond the implications that the complete omission of axillary staging may have on decisions regarding adjuvant systemic therapy, discussed later in this article, certain considerations arise regarding the appropriate type of RT to be integrated within a surgical de-escalation strategy. In the INSEMA and BOOG 2013–08 trials, whole-breast irradiation (WBI) was mandated, whereas in the SOUND trial approximately 80 % of patients received WBI according to local practice. Notably, the eligibility criteria of these studies substantially overlap with those commonly adopted for partial breast irradiation (PBI), despite the fact that clinical trials evaluating PBI have historically required axillary lymph node sampling as an inclusion prerequisite. These observations underscore the lack of robust data guiding radiation volume selection when axillary staging is reduced or omitted. Recent expert consensus further highlights these uncertainties. According to the 2025 St. Gallen International Consensus, opinions remain highly divided on the appropriateness and extent of adjuvant radiation after omission of axillary surgery, with more than 40 % of the panel still favoring WBI in patients eligible for omission of SLNB [8]. A key concern when considering PBI instead of WBI relates to the potential loss of incidental axillary coverage provided by tangential breast irradiation and its possible therapeutic contribution to axillary control. In this regard, relevant insights were provided by data recently presented at the San Antonio Breast Cancer Symposium 2025, reporting the actual radiation dose delivered to axillary levels I–III in patients enrolled in the INSEMA trial. Approximately half of the INSEMA population received a potentially therapeutic dose to axillary level I, defined as median dose of $\geq$ 85 % of the prescribed breast dose. Of note, patients undergoing SLNB received higher incidental axillary doses and more frequent regional nodal irradiation compared with those in whom SLNB was omitted. Collectively, these findings suggest that, within the INSEMA population, omission of SLNB does not seem to require compensatory escalation of axillary irradiation [36].

Adjuvant ribociclib: in some cases, surgical staging of the axilla may optimize patient's selection

In the NATALEE trial, patients with N0 tumors and a tumor size < 2 cm were eligible only in the presence of poor prognostic features (grade 3, grade 2 with Ki67 $\geq$ 20 %, high genomic risk or large tumor size). By contrast, all patients with node-positive disease were eligible. Based on findings from the SOUND, INSEMA and BOOG 2013–08 trials, it has been estimated that omission of SLNB in this setting could exclude approximately 9–11 % of such patients from receiving adjuvant ribociclib. This risk, however, should take into account that in SOUND trial most patients with positive LNs after SLNB had only one LN involved, and considering the overall good prognostic features of enrolled patients, this "upstaging" is unlikely to significantly affect the overall prognosis. Moreover, while the benefit of ribociclib in reducing recurrence risk was consistent across all anatomic stage subgroups (including stage IIA), as discuss above, the NATALEE cohort overall appears high risk, as reflected by the substantial recurrence risk (5y-IDFS 81.0 % and 5y-DDFS 82.5 % in the control arm) [29], the high proportion of patients who received neoadjuvant or adjuvant chemotherapy and the low proportion of grade 1 tumors included (9 %). Therefore, the estimated percentage of patients who may derive a significant benefit from ribociclib after forgoing SLNB may be substantially lower than the estimated 9–11 % (Fig. 3, A). This reinforces the need for refined patient selection to identify those who will derive a meaningful clinical benefit from an escalation strategy, as for many candidates for SLNB omission it would likely constitute overtreatment.

In this context, a clinically useful analysis could be derived from a composite calculation combining the number needed to diagnose from the SOUND, INSEMA, and BOOG 2013–08 trials (i.e. the proportion of patients undergoing SLNB found to have SLN positivity) with the number needed to treat (NNT) extrapolated from the NATALEE trial, similarly to the previously discussed post-hoc analysis of the SENOMAC trial performed to estimate the benefit of ALND in identifying patients eligible for adjuvant abemaciclib. However, applying an NNT-based estimate in the context of adjuvant ribociclib may be overly simplistic and potentially misleading, as NATALEE trial enrolled a heterogeneous population, and the magnitude of benefit across different risk and nodal burden subgroups remains incompletely defined. Indeed, while NNT provides a useful population-level estimate of treatment effect, it may fail to adequately capture individual patient risk.

Genomic assay testing: applicability in the absence of sentinel lymph node biopsy

Another controversial issue is represented by the use of genomic assays in the context of axillary surgery omission, as genomic testing was not incorporated in any of the trials evaluating SLNB omission. Genomic

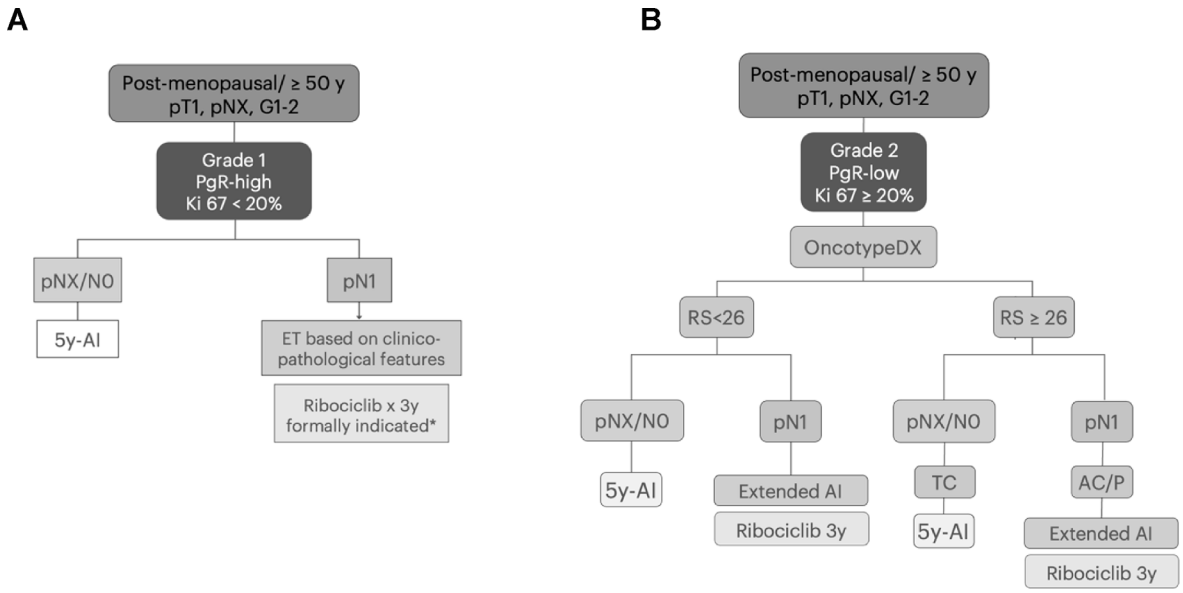

Fig. 3. Possible treatment algorithm for patients with luminal EBC who meet criteria for omission of SLNB and present low-risk (A) and high-risk (B) biological features, with either unknown or confirmed nodal status. RS: Recurrence Score; AI: Aromatase Inhibitor; TC: Docetaxel/Cyclophosphamide; AC: Anthracyclines/Cyclophosphamide; P: paclitaxel; y: year. * The overall benefit–risk balance of adjuvant ribociclib should be discussed in such cases, as advising ribociclib in all patients with pN1 disease and low risk biological characteristics may carry a risk of overtreatment.

tests have become useful tools in clinical practice, offering prognostic and predictive information in patients with luminal EBC [37]. Axillary nodal status is one of the variables guiding the decision to use a genomic test. Current guidelines recommend Oncotype DX, MammaPrint, EndoPredict, and the Breast Cancer Index for postmenopausal women with up to three positive lymph nodes, whereas Prosigna is limited to node-negative disease [38]. Based on the TAILORx trial, premenopausal women with node-negative disease may be offered the Oncotype DX assay, with adjuvant chemotherapy considered for those with a RS $\geq$ 16, depending on clinical risk [39]. Conversely, there is insufficient evidence to support the use of genomic testing in younger patients (<50 years) with node-positive disease. In light of these considerations, ASCO guidelines support the use of genomic testing, specifically Oncotype DX, even in the absence of SLNB [24]. However, the information on SLNB may inform the choice of adjuvant chemotherapy schema, with a possible chemotherapy intensification (i.e anthracyclines prescription) in patients with high genomic risk and lymph nodes involvement. Furthermore, the utility of genomic testing diminishes with increasing axillary disease burden; in patients with four or more positive ALNs, genomic testing is not advised due to the absence of evidence supporting its use. In these cases, nodal status is critical for identifying high-risk patients who would already qualify for escalated adjuvant therapy based on standard clinicopathologic criteria. Nevertheless, the likelihood of pN2 disease in the populations of SOUND and INSEMA trials is extremely low (0.6 % and 0.2 %, respectively) suggesting that the omission of axillary surgery in these settings rarely leads to a clinically significant underestimation of nodal burden.

Omission of sentinel lymph node biopsy: yes, with selected exceptions

Bringing together the abovementioned considerations and current guidelines, it becomes essential to identify the specific cases in which an accurate axillary staging remains necessary to personalize systemic therapy and improve clinical outcomes in patients with luminal EBC.

Another open issue remains the possible difference in histopathological features between initial biopsy and final histology, possibly due to the spatial heterogeneity of the tumor. In patients who meet the criteria for SLNB omission based on initial biopsy, but whose final histopathology reveals unfavorable biological features, such as low PgR and high Ki67 index, a genomic testing (Fig. 3, B). In such instances, more detailed information on the extent of nodal disease may influence the choice of the best adjuvant therapy strategy, including chemotherapy options (i.e possible addition of anthracyclines) or addition of adjuvant CDK4/6 inhibitors. In these scenarios, multidisciplinary discussion and truly shared decision-making are fundamental. It is important to clearly communicate with patients about the balance between potential benefits and risks, the possible comorbidities associated with axillary surgical staging and the implications of escalating systemic therapy. A transparent conversation helps ensure that patients understand how each option may affect not only survival outcomes but also theirQoL. At the same time, ongoing clinical studies are evaluating whether neoadjuvant treatment strategies can be more precisely individualized through genomic risk assessment performed directly on biopsy specimens [40]. Having access to this molecular information at the outset could significantly refine both surgical planning and systemic therapy choices, allowing clinicians to better match treatment intensity to the biological characteristics of each tumor.

Conclusions

Taken together, the results of studies on axillary de-escalation, along with the considerations presented in this review, lead to a single conclusion: advancing understanding and integration of biologic predictors, together with an expanding array of effective adjuvant therapies, are making invasive nodal staging avoidable in selected cases. In this context, AUS has emerged as a valuable non-invasive modality to guide treatment planning. The studies discussed above demonstrate excellent diagnostic accuracy of AUS for nodal staging; however, its operator-dependent nature underscores the importance of performing radiologic assessment in high-volume centers to minimize false-negative results. Alongside AUS, additional non-invasive strategies are being explored to further refine nodal assessment. Among these, hybrid [^{18}F] FDG PET/MRI has demonstrated encouraging sensitivity in detecting macrometastatic ALNs in patients deemed cN0 by AUS [41]. Within this evolving framework, increasingly sophisticated and integrative imaging approaches, including advanced radiomics-based models, represent an additional step toward the progressive replacement of surgical axillary staging by non-invasive imaging strategies [42].

Looking ahead, future perspectives focus on the complete omission of breast surgery in women achieving an image-guided vacuum-assisted breast biopsy (VABB)-determined pathological complete response after neoadjuvant therapy. In this setting, the refinement of minimally invasive radiologic techniques, combined with advances in molecular diagnostics including liquid biopsy, may eventually replace invasive procedures for detecting minimal residual disease and enable more precise tailoring of oncologic treatment.

The change in perspective regarding the axillary management for EBC understandably raises concern among clinicians, as many cN0 patients are upstaged to N + at surgery; yet, long-term outcomes largely remain unchanged, and the benefits in terms of lower surgical morbidity, improved QoL, and better cosmetic results are clear. The advent of effective systemic therapies for high-risk disease reduces concerns about residual axillary disease, but in selected cases increases the need for finer risk stratification, for which axillary staging may still be informative. Accordingly, while omission of axillary surgery often does not worsen overall outcomes, decisions should be made within a patient-centered, multidisciplinary framework to ensure that de-escalation does not compromise oncologic safety.

Declaration of competing interest

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