Editorial Commentary

Should abemaciclib candidacy be an indication for ALND?—commentary on SENOMAC post-hoc analysis

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Modern treatment of early-stage breast cancer centers on multimodal individualized treatment that considers tumor- and patient-specific factors within the context of a multidisciplinary team. Evidence-based personalized treatment not only improves survival but also minimizes morbidity without compromising oncologic outcomes (1). This approach is most notably demonstrated by changes in axillary nodal management over the past two decades, resulting in sentinel lymph node biopsy (SLNB) becoming standard for surgical axillary staging in patients with clinically node-negative (cN0) disease, while indications for axillary lymph node dissection (ALND) have decreased (1).

Surgical axillary staging provides prognostic information and can influence adjuvant therapy recommendations (2), but the extent of axillary surgery does not alter survival (3-6). In patients with cT1–2 cN0 invasive breast cancer with low volume axillary disease (<3 positive nodes) on SLNB, the American College of Surgeons Oncology Group (ACOSOG) Z0011 and After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS) trials showed that SLNB combined with either whole breast or regional-nodal radiation was non-inferior in terms of overall survival (OS) and offered comparable locoregional control compared to completion ALND (cALND) in patients undergoing breast-conserving surgery (BCS) and mastectomy (5-7). Though impactful, Z0011 and AMAROS were limited by variations in radiation fields and eligibility criteria, including tumor size (cT1–2), patient sex, presence of extranodal extension, and the low number of patients undergoing mastectomy in AMAROS (8). Thus, the sentinel node-macrometastasis (SENOMAC) trial was designed to validate these findings within a broader patient population (8).

SENOMAC was a prospective randomized phase-3 non-inferiority trial conducted at 67 European hospitals from January 2015 to December 2021 that enrolled 2,766 women and men with cT1–3cN0 invasive breast cancer who were found to have 1–2 SENOMAC on SLNB. They were randomized to cALND or omission of ALND (i.e., SLNB alone). All patients underwent adjuvant systemic and radiation therapy. After a median of 46.8 months, the estimated 5-year recurrence-free survival was 89.7% [95% confidence interval (CI): 87.5–91.9] with SLNB alone vs 88.7% (95% CI: 86.3–91.1) with ALND, demonstrating that ALND omission was non-inferior to cALND (8). These findings support that SLNB alone is a reasonable option for patients with early-stage invasive breast cancer and low-volume axillary disease. However, a recently published post-hoc analysis of the SENOMAC trial

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investigated the utility of cALND in providing an indication for the use of novel adjuvant cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors in patients with hormone-receptor positive (HR^+) human epidermal growth factor 2 (HER2) negative ($HER2^-$) disease (1).

Oral CDK4/6 inhibitors (i.e., abemaciclib, ribociclib, palbociclib) can be used in addition to endocrine therapy (ET) in the treatment of $HR^+/HER2^-$ breast cancer. CDK4/6 inhibitors improve progression-free survival when used in combination with ET in the metastatic setting (9), and their utility in extending OS in patients with high-risk early-stage breast cancer is under investigation in the monarchE and NATALEE trials (10,11). While the addition of CDK4/6 inhibitors to standard ET has shown an absolute reduction in invasive distant recurrence (11) and invasive disease-free survival for women with high-risk $HR^+/HER2^-$ early breast cancers (10,11), the final endpoint of OS has not yet matured. A recent post-hoc analysis of the SENOMAC trial sought to elucidate benefit versus harm in performing cALND in select patients with $HR^+/HER2^-$ disease to identify patients who may be eligible for adjuvant abemaciclib. SENOMAC patient-reported outcome (PRO) data regarding arm dysfunction and AMAROS data regarding clinical signs and treatment of lymphedema were used to determine the expected rate of arm impairment and lymphedema after cALND (1). These data, in combination with 5-year invasive disease-free survival results from the monarchE trial, were used to calculate 3 values in the post-hoc analysis: (I) number needed to treat (i.e., number of patients who need to receive adjuvant abemaciclib to avoid one invasive disease-free survival event), (II) number needed to diagnose (i.e., number of cALNDs needed to perform to identify ≥4 nodal metastases and thus provide an indication for adjuvant abemaciclib per monarchE criteria); and (III) number needed to harm (i.e., number of patients needing to undergo cALND in order to have one additional report of either severe or very severe arm impairment or clinical signs or treatment of lymphedema) (1).

MonarchE was an open-label randomized trial investigating the impact of adjuvant abemaciclib in addition to standard ET alone on outcomes in patients at high-risk of distant recurrence with $HR^+/HER2^-$ breast cancer (11). The only indication for adjuvant abemaciclib for monarchE cohort 1 [patients who were ≥18 years with estrogen receptor positive (ER^+)/$HER2^-$, pT1–2, grade 1–2 breast cancer with 1–2 SLN(s) macrometastases] was the presence of ≥4 axillary nodal metastases, which would theoretically only be known if patients received a cALND (1). Thus, the SENOMAC post-hoc analysis explored the potential impact of cALND on patients enrolled in SENOMAC who also matched the criteria for cohort 1 of monarchE and could potentially become eligible for adjuvant abemaciclib after cALND if ≥4 axillary nodal metastases were identified.

Sixty-seven percent (n=1,705) of SENOMAC trial patients met eligibility criteria for the post-hoc analysis (1). Of these patients, 802 (47%) underwent cALND and 903 (53%) had SLNB alone. There were similar survey response rates for the PRO arm function questionnaire in both groups (83% cALND *vs.* 82% SLNB alone). After a median follow-up of 45.2 months, there was an increase of severe or very severe arm dysfunction in patients undergoing cALND compared to those undergoing SLNB alone [84/634 (13%) *vs.* 30/708 (4%); P<0.001]. They calculated that 104 patients would need to undergo cALND in order to avoid one invasive disease-free survival event at 5 years with 2 years of adjuvant abemaciclib treatment. Of those 104 patients, 9 would develop severe or very severe arm impairment, 13 would develop clinical signs of lymphedema, and 17 would require lymphedema treatment (1). The authors conclude that, given this significant risk of arm impairment and no known OS benefit from adjuvant abemaciclib, performing cALND to identify patients with ≥4 nodal metastases should not be routinely performed.

The authors' recommendation against routine performance of cALND in this patient population reflects the overall trend in de-escalation of axillary surgery for breast cancer patients. Since Z0011 and AMAROS, SLNB has been adopted as the standard for surgical axillary staging in clinically node negative (cN0) patients. The Choosing Wisely and American Society of Clinical Oncology (ASCO) Guidelines recommend against the routine use of SLNB in women ≥70 years of age with HR+ invasive breast cancer (12). More recently, the Sentinel Node vs Observation After Axillary Ultra-Sound (SOUND) and Intergroup-Sentinel-Mamma (INSEMA) trials used pre-operative axillary ultrasound to stage the axilla in patients with early-stage disease. Short-term results demonstrate that SLNB can safely omitted in patients with cT1–2 cN0 breast cancer and a negative pre-operative axillary ultrasound (13,14). Long-term results await maturation and additional ongoing studies will further provide data to inform SLNB omission (15,16). As data continues to support omission of surgical nodal staging, the notion that patients with favorable tumor biology should undergo ALND to inform use of adjuvant abemaciclib is a difficult argument for surgeons and patients. While the burden of additional nodal disease

can be identified by further surgery (i.e., cALND), several nomograms exist that can calculate the probability of non-sentinel lymph node (SLN) metastases and potentially spare patients further surgery (17,18). Use of these nomograms can support identifying patients who are likely to have ≥4 axillary nodal metastases and are thereby eligible for adjuvant abemaciclib without performing cALND. However, for patients with clinically node positive (cN+) disease who undergo upfront surgery, ALND remains standard of care. Other indications for ALND include patients with inflammatory breast cancer, patients found to have more than ≥3 positive SLNs, those who are not suitable radiation therapy candidates, and residual nodal disease after neoadjuvant chemotherapy (2).

The size of SLN metastases is an independent predictor of the presence of non-SLN metastases (17,18). While the presence of any residual axillary disease after neoadjuvant chemotherapy has been an indication for cALND (19), recent data support the omission of cALND in patients with only isolated tumor cells (ITCs) in the SLN(s) after neoadjuvant chemotherapy (20). Additionally, the results of Alliance A11202, which investigates the use of axillary radiation alone rather than cALND with axillary radiation in patients with residual nodal disease after chemotherapy, will further inform the utility of cALND in the neoadjuvant setting. While size of SLN metastases is understood as an important factor for predicting total burden of axillary disease and performance of cALND, the definition of lymph node positivity (i.e., whether macrometastases, micrometastases, or ITCs) was not specified in monarchE (11) and should be carefully considered in treatment recommendations.

While the use of oral abemaciclib in addition to standard ET in high-risk patients with $HR^+/HER2^-$ breast cancer provides some benefits, there are several important considerations. Advocating for more aggressive axillary surgery without a clear OS advantage for those who receive abemaciclib should be approached cautiously, especially in the setting of adding morbidity. Abemaciclib itself can result in morbidity. Common side effects of abemaciclib include hematologic and liver enzyme derangements, diarrhea, interstitial lung disease, and fatigue (11). When comparing abemaciclib plus ET to the ET alone in monarchE, there were more grade ≥3 adverse events and serious adverse events in patients receiving abemaciclib (49.9% abemaciclib *vs.* 16.9% ET alone) (11). Adverse events caused interruption of abemaciclib in 61.7% of patients, and 43.6% of patients required abemaciclib dose-reduction due to side effects (11). While there were similar deaths due to adverse events while on treatment in both groups, 2 (2/15) deaths in the abemaciclib group were assessed as possibly directly related to study treatment, while none of the deaths in the ET group were thought to be treatment related (11).

The morbidity of ALND is well-established. Patients who receive SLNB alone have less arm morbidity and improved quality of life compared to those who undergo ALND (21). Breast cancer-related lymphedema (BCRL) is one of the most dreaded outcomes of axillary surgery, as it is often a lifelong condition with substantial physical and psychological impact on patients (21). Extent of axillary surgery is associated with increased rates of BCRL—25–30% of patients develop lymphedema after ALND compared to about 8–11% of patients after SLNB (22). Body mass index (BMI) is a well-established risk factor for BCRL (22,23). There have also been racial/ethnic disparities noted with higher rates of BCRL in Black and Hispanic individuals, though the biological basis for this is unknown (23,24). Patient BMI, race, and ethnicity were not reported in the post-hoc analysis, though these factors could be informative given reported differences in BCRL rates. Though no gold standard exists for the evaluation or treatment of BCRL, patient-reported symptoms taken together with physical exam and quantitative metrics, including linear circumference and volumetric and bioimpedance measures, can aid in diagnosis (21). However, patient perception does not always correlate with objective measurements. Patients have been shown to both over- and underreport perception of BCRL symptoms. In a study including 120 patients undergoing either SLNB or ALND followed for 12 months with both PRO of arm function and arm volume measurements, 12% of patients reported a sensation of arm swelling with no change in arm volume while 5% of patients were found to meet volume criteria for lymphedema without any subjective arm dysfunction (25). Arm volumes were also found to fluctuate over the study period, underscoring the need for longitudinal follow-up (25). Because of these known limitations in the diagnosis of BCRL, longitudinal quantitative measures of arm volumes in addition to PRO data would have strengthened the post-hoc analysis.

With no data on an OS benefit with adjuvant abemaciclib for patients with non-metastatic $HR^+/HER2^-$ breast cancer and the increased morbidity of ALND, we agree with the authors of the SENOMAC post-hoc analysis that routine cALND should not be routinely performed for patients with cT1–2N0, $HR^+/HER2^-$ breast cancer found to have 1–2 positive SLN(s). While axillary surgery can provide

prognostic information, its utility is becoming increasingly reduced for patients with $HR^+/HER2^-$ disease due to genomic assays and recent data revealing that omission of SLNB in select patients does not influence OS. Increasing breast cancer morbidity with more extensive axillary surgery to inform the use of oral systemic therapy that may not result in an OS benefit is overtreatment and not currently warranted.

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Footnote

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