Completion axillary lymph node dissection for the identification of pN2–3 status as an indication for adjuvant CDK4/6 inhibitor treatment: a post-hoc analysis of the randomised, phase 3 SENOMAC trial

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Summary

Background In luminal breast cancer, adjuvant CDK4/6 inhibitors (eg, abemaciclib) improve invasive disease-free survival. In patients with T1–2, grade 1–2 tumours, and one or two sentinel lymph node metastases, completion axillary lymph node dissection (cALND) is the only prognostic tool available that can reveal four or more nodal metastases (pN2–3), which is the only indication for adjuvant abemaciclib in this setting. However, this technique can lead to substantial arm morbidity in patients. We aimed to pragmatically describe the potential benefit and harm of this strategy on the individual patient level in patients from the ongoing SENOMAC trial.

Methods In the randomised, phase 3, SENOMAC trial, patients aged 18 years or older, of any performance status, with clinically node-negative T1–T3 breast cancer and one or two sentinel node macrometastases from 67 sites in five European countries (Denmark, Germany, Greece, Italy, and Sweden) were randomly assigned (1:1), via permutated block randomisation (random block size of 2 and 4) stratified by country, to either cALND or its omission (ie, they had a sentinel lymph node biopsy only). The primary outcome is overall survival, which is yet to be reported. In this post-hoc analysis, patients from the SENOMAC per-protocol population, with luminal oestrogen-receptor positive, HER2-negative, T1–2, histological grade 1–2 breast cancer, with tumour size of 5 cm or smaller were selected to match the characteristics of cohort 1 of the monarchE trial who would only have an indication for adjuvant abemaciclib if found to have 4 or more nodal metastases. The primary study objective was to determine the number of patients who developed patient-reported severe or very severe impairment of physical arm function after cALND (as measured by the Lymphedema Functioning, Disability, and Health [Lymph-ICF] Questionnaire) 1 year after surgery to avoid one invasive disease-free survival event at 5 years with 2 years of adjuvant abemaciclib, using invasive disease-free survival event data from cohort 1 of the monarchE trial. The SENOMAC trial is registered with ClincialTrials.gov, NCT02240472, and is closed to accrual and ongoing.

Findings Between Jan 31, 2015, and Dec 31, 2021, 2766 patients were enrolled in SENOMAC and randomly assigned to cALND (n=1384) or sentinel node biopsy only (n=1382), of whom 2540 were included in the per-protocol population. 1705 (67%) of 2540 patients met this post-hoc study's eligibility criteria, of whom 802 (47%) had a cALND and 903 (53%) had a sentinel lymph node biopsy only. Median age at randomisation was 62 years (IQR 52–71), 1699 (>99%) of 1705 patients were female, and six (<1%) were male. Among 1342 patients who responded to questionnaires, after a median follow-up of 45·2 months (IQR 25·6–59·8; data cutoff Nov 17, 2023), patient-reported severe or very severe impairment of physical arm function was reported in 84 (13%) of 634 patients who had cALND versus 30 (4%) of 708 who had sentinel lymph node biopsy only (χ^2 test p<0·0001). To avoid one invasive disease-free survival event at 5 years with adjuvant abemaciclib, cALND would need to be performed in 104 patients, and would result in nine patients having severe or very severe impairment of physical arm function 1 year after surgery.

Interpretation As a method to potentially identify an indication for abemaciclib, and subsequently avoid invasive disease-free survival events at 5 years with 2 years of adjuvant abemaciclib, cALND carries a substantial risk of severe or very severe arm morbidity and so cALND should be discouraged for this purpose.

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Research in context

Evidence before this study

We searched PubMed on Oct 13, 2023, and again on March 30, 2024, for English-language studies published since database inception, using the terms "abemaciclib", "CDK4/6 inhibitor", "randomized trial", "axillary surgery", and "axillary (lymph node) dissection", presenting trial results for the addition of CDK4/6 inhibitors to adjuvant endocrine treatment in luminal HER2-negative breast cancer, or discussing the potential effect of such trial results on axillary surgery practice. Studies regarding the use of CDK4/6 inhibitors in the neoadjuvant or metastatic setting were disregarded. We identified multiple publications of the monarchE trial and, more recently, the NATALEE trial. We deduced that only the monarchE trial eligibility criteria created a clinical dilemma by necessitating a completion axillary lymph node dissection (cALND) in patients with grade 1–2 breast tumours that were smaller than 5 cm in diameter and one or two sentinel lymph node metastases, such that they would only have an indication for adjuvant abemaciclib in the case of identification of four or more axillary nodal metastases. We identified only two commentaries on the subject, discussing the value and potential consequences of such an increased use of cALND after a positive sentinel lymph node biopsy, but no studies reporting on the effect of such practices for the patients. Given the increasing evidence that cALND does not provide a survival benefit for patients with one or two metastases in their sentinel lymph node biopsy, and the resulting efforts of clinicians to de-escalate axillary surgery and thus reduce patients' impairment of arm function and the incidence of arm lymphoedema, we aimed to pragmatically describe the potential benefits and harms that patients would be exposed to if receiving a cALND with the aim of identifying the few individuals with four or more nodal metastases.

Added value of this study

By use of data from the per-protocol population of the large, international, randomised, non-inferiority SENOMAC trial, we identified a significantly increased occurrence of patient-reported and objectively measured arm morbidity among patients exposed to cALND, and a small change of improving oncological outcomes with treatment with adjuvant abemaciclib. By presenting numbers needed to treat, diagnose, and harm, we provide easily applicable and pragmatic data that can be used in the discussion with patients who need to understand their risks and potential benefits when confronted with the option of more extensive axillary surgery.

Implications of all the available evidence

The present analysis provides unique, patient-focused, clinically relevant data that weigh survival outcomes from the monarchE trial against arm morbidity data from the SENOMAC and AMAROS trials. We propose that the high number of patients potentially developing severe arm morbidity after a cALND, among whom very few will have any oncological benefit as a result, clearly disqualifies this staging tool for the identification of candidates for adjuvant abemaciclib.

Introduction

Nodal status is a strong prognostic factor in breast cancer. Before the clinical implementation of sentinel lymph node biopsy, pathological nodal status in clinically node-negative patients was determined by axillary lymph node dissection (ALND), with substantial consequences for arm morbidity and quality of life.[1] ALND provides detailed information on the number of affected nodes, whereas sentinel lymph node biopsy offers less complete nodal staging. Multiple attempts have been made to de-escalate surgical staging of the axilla, and since the implementation of sentinel lymph node biopsy the number of clinical indications for a completion ALND (cALND; ie, an ALND after sentinel node biopsy) has been substantially reduced.[1–4] This reduction in clinical indications for cALND is especially relevant in this era, when survival in breast cancer has increased substantially, and more focus is being given to aspects of survivorship, such as quality of life. The potential benefits of a cancer treatment should thus be weighed against its functional, physical, and psychosocial consequences.

In patients with clinically node-negative breast cancer who have one or two sentinel lymph node metastases, cALND does not improve survival.[1–4] This is despite the fact that patients with four or more nodal metastases (pN2–3 status; 13·7% and 12·9% after cALND in ACOSOG Z0011 and AMAROS, respectively), who might have an indication for intensified adjuvant treatment strategies, remain unidentified if they have a sentinel lymph node biopsy only. Importantly, arm lymphoedema and patient-reported arm swelling is significantly less common after axillary radiotherapy than after cALND.[1,5]

In the monarchE[6,7] and NATALEE[8] trials, the addition of adjuvant CDK4/6 inhibitors to standard endocrine therapy resulted in improved invasive disease-free survival. The recently published NATALEE trial[8] included patients with both node-positive and node-negative luminal HER2 (also known as ERBB2)-negative breast cancer to evaluate survival benefits through the addition of adjuvant ribociclib to endocrine treatment, the monarchE trial, which tested the CDK4/6 inhibitor abemaciclib, limited enrolment to only high-risk patients.[9] High risk in the monarchE trial was defined as either pathological N stage 2–3 (pN2–3) or one-to-three nodal metastases (pN1) in combination with additional risk factors—namely, histological grade 3 or tumour size larger than 5 cm. Hence, in patients with luminal HER2-negative breast cancer undergoing primary surgery that identified one-to-three nodal metastases, but without additional risk factors, a cALND might need to

be performed to identify candidates for adjuvant abemaciclib. The consequences of such an escalation of axillary surgery have not been evaluated from a perspective of clinically relevant arm morbidity.[10,11]

The international SENOMAC trial randomly assigned patients with clinically node-negative breast cancer and one or two sentinel lymph node macrometastases to cALND or its omission (ie, sentinel lymph node biopsy only). The primary endpoint of overall survival has not yet been reported, but non-inferiority regarding recurrence-free survival has been published, showing non-inferiority of the omission of cALND,[12] and 1-year patient-reported outcome measures showed significantly worse arm morbidity after cALND compared with sentinel lymph node biopsy alone.[13] Here, we aimed to weigh the numbers needed to diagnose by cALND to identify individuals with pN2–3 against (1) the number needed to treat for avoiding one invasive disease-free survival event at 5 years after completing 2 years of adjuvant abemaciclib and (2) the number needed to harm regarding severe or very severe patient-reported arm morbidity at 1 year and arm lymphoedema at 5 years.

Methods

Study design and participants

The randomised, phase 3 SENOMAC trial included patients aged 18 years or older of any performance status, both female and male (as defined by personal identity numbers), with clinically node-negative T1–T3 breast cancer and one or two sentinel node macrometastases from 67 sites in five European countries (Denmark, Germany, Greece, Italy, and Sweden). All patients provided informed written consent. The trial was registered at ClinicalTrials.gov, NCT02240472, and the protocol has been published elsewhere.[14] The trial was approved by the Swedish Ethical Review Authority (2014/1165-31/1) and relevant Ethical Review Boards in participating countries and was performed and monitored according to Good Clinical Practice.

For this post-hoc analysis, patients aged 18 years and older undergoing primary surgery for luminal, oestrogen receptor-positive, HER2-negative, T1–T2 breast cancer (ie, ≤5 cm in diameter), and histological grades 1 or 2 were selected from the per-protocol population of the SENOMAC trial, to match the eligibility criteria for the cohort 1 of the monarchE trial, who would only have an indication for adjuvant abemaciclib if found to have four or more nodal metastases.[6] The per-protocol population included patients who had not withdrawn their informed consent within 21 days from randomisation, had received the axillary surgery they were randomly assigned to, and had not violated eligibility criteria at enrolment. A pre-operative axillary ultrasound was mandatory. Exclusion criteria for SENOMAC were previous invasive breast cancer, regional or distant metastases, bilateral breast cancer if one side met exclusion criteria, medical contraindications against radiotherapy or systemic treatment, or an inability to understand the study information. The present analysis was not specified in the SENOMAC trial protocol but designed post-hoc and was not affected by any protocol amendments.

Procedures

Full details of the SENOMAC procedures have been published elsewhere.[12,13] Briefly, all provisionally eligible patients underwent sentinel lymph node biopsy showing one or two macrometastases, and were then randomly assigned (1:1) to cALND or its omission (ie, they had a sentinel lymph node biopsy only) using permutated block randomisation (random block size of 2 and 4), stratified by country.

Adjuvant systemic therapy, including adjuvant radiotherapy, was given in accordance with national guidelines.

All patients completed questionnaires regarding health-related quality of life and long-term complications to the arm (the EORTC Quality of Life Questionnaire [QLQ-C30], the breast cancer-specific QLQ-BR23 questionnaire, the EuroQol Group 5-Dimension questionnaire, and the Lymphedema Functioning, Disability, and Health Questionnaire [Lymph-ICF questionnaire[15]]) at enrolment and will continue to complete them at 1, 3, 5, and 10 years after surgery. No clinical measures of lymphoedema were done.

For the present analysis of arm morbidity, 1-year patient-reported outcome measures using the Lymph-ICF questionnaire were extracted from the SENOMAC database. The Lymph-ICF questionnaire, specifically addressing impairment of arm function and activity limitations, includes 29 questions producing a total score and five separate domains (physical function, mental function, household activities, mobility activities, and social activities). Each question is answered on a visual analogue scale and renders scores from 0 to 100, where higher numbers indicate worse arm morbidity.[16] Domain scores are calculated as the average of all non-missing individual items that belong to the relevant domain, and the total score takes all items into account. No central review of domain scores was done.

Outcomes

In the SENOMAC study, the primary endpoint is overall survival. For the present post-hoc analysis, the primary objective was the number of patients developing patient-reported severe or very severe impairment of physical arm function after cALND as measured by the Lymph-ICF questionnaire 1 year after surgery to avoid one invasive disease-free survival event at 5 years with 2 years of adjuvant abemaciclib using data on invasive disease-free survival from cohort 1 of the monarchE trial. To obtain this number, the numbers needed to treat, numbers needed to diagnose, and numbers needed to harm were calculated separately.

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See Online for appendix

Secondary objectives were the expected rate of clinical arm lymphoedema at 5 years and treatment for arm lymphoedema during 5 years postoperatively using published data from the AMAROS trial,[1] which randomly assigned patients with breast cancer and one or two sentinel lymph node metastases to cALND or axillary radiotherapy.

Statistical analysis

The number needed to treat estimates how many individuals would need to receive a treatment to avoid one negative event and is the inverse of the absolute risk reduction.[17,18] The absolute risk reduction is the control event rate minus the experimental event rate, and thus number needed to treat is equivalent to 1 divided by the absolute risk reduction. Number needed to treat is rounded to the nearest whole number. Relevant figures were extracted from the recently published 5-year results of the monarchE trial on invasive disease-free survival (ie, an event was any death, ipsilateral or contralateral invasive breast cancer recurrence, or secondary invasive cancer). Only cohort 1 of monarchE was considered (n=5120), which included patients with either four or more nodal metastases or one-to-three nodal metastases in combination with either grade 3 or a tumour of larger than 5 cm in diameter, who were randomly assigned (1:1) to adjuvant abemaciclib and endocrine treatment or to endocrine treatment alone.[7] We chose to only use cohort 1 of the monarchE trial because cohort 2 was smaller (n=517) and was based on centrally determined Ki67 of 20% or more and the SENOMAC trial did not integrate a central review of Ki67 and so could not allow for adequate matching. Additionally, the US Food and Drug Administration (FDA) approval of abemaciclib, which was initially restricted to patients with a Ki67 of more than 20% in 2021, was updated in March, 2023, to remove the Ki67 testing requirement, and most guidelines do not take Ki67 into account when defining indications for adjuvant abemaciclib.

The number needed to diagnose calculates the number of patients who need to undergo a diagnostic or staging procedure—in this case a cALND—to identify one additional individual with the state of interest—in this case four or more nodal metastases. Here we calculated number needed to diagnose as 1 divided by the difference between the proportion of patients with four or more nodal metastases in the cALND group and the corresponding proportion in the sentinel lymph node biopsy alone group.

The number needed to harm estimates how many individuals would need to be exposed to a potentially harmful treatment until one additional negative event is observed, and is the inverse of the absolute risk increase.[19] Like the absolute risk reduction, the absolute risk increase is the control event rate minus the experimental event rate, only that events are specified to be negative events (ie, deaths and adverse events). Number needed to harm is rounded to the nearest whole number. Number needed to harm was calculated via two different strategies: (1) as the number of eligible patients in SENOMAC who needed to undergo a cALND to get one negative event, defined as patient-reported severe or very severe impairment of physical arm function, which was chosen since it most closely resembles symptoms of arm lymphoedema, and (2) as the number of patients from AMAROS who needed to undergo a cALND to get one negative event, defined as either clinical signs of lymphoedema at 5 years or treatment for arm lymphoedema at any time during 5 years of follow-up. Updated AMAROS follow-up data on 5-year arm morbidity were published in 2022 (frequencies on lymphoedema found in the data supplement of the AMAROS publication).[1]

The primary endpoint of the SENOMAC trial itself, overall survival, has not yet been reported. The hypothesis is that overall survival will not be worsened by more than 2·5% after 5 years, corresponding to a hazard ratio not exceeding 1·44 when comparing sentinel lymph node biopsy alone with cALND. For the trial to have 80% power with a one-sided α of 10%, a total of 190 deaths need to occur with a target accrual of 3000 patients.[12]

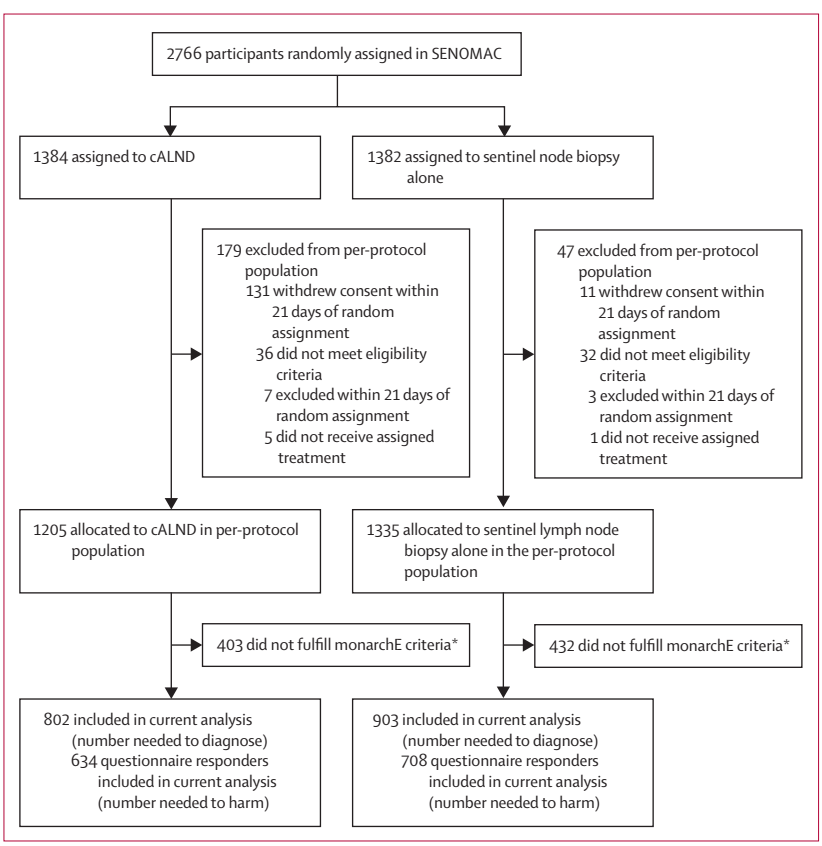

Figure: **Inclusion of participants from the SENOMAC trial in the current analysis**
*monarchE criteria were oestrogen-receptor positive, HER2-negative, tumour size of ≤5 cm, and histological grade 1–2. In addition to the selected original SENOMAC subpopulation, 5-year arm lymphoedema rates were based on the reported clinical sign of lymphoedema in 101 (24·5%) participants in the cALND group and in 45 (11·9%) in the axillary radiotherapy group of the AMAROS trial.[1] cALND=completion axillary lymph node dissection.

Descriptive variables are presented as frequencies and percentages in the case of categorical variables, and as mean (SD) or median (IQR) for continuous variables. Lymph-ICF domain scores were categorised according to the severity of arm morbidity into no or a small problem (score of 0 to <25), a moderate problem (score of 25 to <50), and a severe or very severe problem (score of 50 to 100). Results are presented as numbers and proportions among responders in each category, and mean (SD) score per domain. The distribution of categories over the randomisation groups was tested with the two-sided χ^2 test. Mean values were compared using Student's *t* test. The questionnaire response rate was calculated by dividing the number of completed questionnaires by the number of individuals who had the opportunity to complete the questionnaire. Patients who had opted out of completing questionnaires due to language difficulties or other reasons, or those treated at sites that did not distribute questionnaires in the trial, were not counted as potential responders. The significance level was adjusted for multiple testing for Lymph-ICF results using a Bonferroni correction, such that p values equal to 0·0087 or less were considered to be significant.

All statistical analyses were performed using R (version 4.1.2).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 31, 2015, and Dec 31, 2021, 2766 patients were enrolled in SENOMAC and were randomly assigned to cALND (n=1384) or sentinel node biopsy only (n=1382), of whom 2540 were included in the SENOMAC per-protocol population. For this analysis, we included 1705 (67%) of 2540 patients of the SENOMAC per-protocol population who had received primary surgery, of whom 903 (53%) had been assigned to sentinel lymph node biopsy alone and 802 (47%) had been assigned to cALND (figure). As of data cutoff (Nov 17, 2023), median follow-up was 45·2 months (IQR 25·6–59·8). Median age at randomisation was 62 years (IQR 52–71), 1699 (>99%) of 1705 patients were female, and six (<1%) were male. Baseline clinical and disease characteristics are shown in table 1. Race, ethnicity, and self-reported gender were not registered.

The questionnaire response rate for the Lymph-ICF questionnaire at 1 year of follow-up was 82·4% with 1342 of 1629 potential responders, 634 (83%) of 764 in the cALND group and 708 (82%) of 865 in the sentinel lymph node biopsy only group. The domains of physical function, mental function, mobility activities, and the total score showed significant differences between the groups on both statistical tests, with the sentinel lymph node biopsy group having significantly better outcomes

	Completion axillary lymph node dissection group (N=802)	Sentinel lymph node biopsy alone group (N=903)
Age, years		
<65	451 (56%)	529 (59%)
≥65	351 (44%)	374 (41%)
Median	62 (53–70)	62 (52–71)
Sex		
Female	800 (>99%)	899 (>99%)
Male	2 (<1%)	4 (<1%)
Tumour size, mm	20·3 (9·8)	21·5 (10·0)
Tumour stage		
T1 (≤20 mm)	493 (61%)	521 (58%)
T2 (21–50 mm)	309 (39%)	382 (42%)
Sentinel node macrometastases		
1	674 (84%)	770 (85%)
2	128 (16%)	133 (15%)
Number of lymph nodes removed	15·5 (7·0)	2·3 (1·5)
Number of axillary metastases	2·2 (2·4)	1·3 (0·5)
Breast surgery		
Breast-conserving surgery	564 (70%)	612 (68%)
Mastectomy	238 (30%)	291 (32%)
Tumour histological type		
Invasive carcinoma of no specific type	621 (77%)	669 (74%)
Lobular carcinoma	157 (20%)	200 (22%)
Other	24 (3%)	34 (4%)
Nottingham histological grade		
Grade 1	199 (25%)	233 (26%)
Grade 2	603 (75%)	670 (74%)
Lymphovascular invasion		
Yes	190 (24%)	215 (24%)
No	609 (76%)	676 (75%)
Missing	3 (<1%)	12 (1%)
Ki67 score		
Mean	18·7 (12·1)	19·2 (12·5)
Missing	11 (1%)	10 (1%)
Adjuvant chemotherapy*		
Yes	447 (56%)	470 (52%)
No	349 (44%)	428 (47%)
Missing	1 (<1%)	0
Adjuvant endocrine therapy*		
Yes	785 (98%)	878 (97%)
No†	11 (1%)	20 (2%)
Missing	1 (<1%)	0
Radiotherapy*		
None	41 (5%)	36 (4%)
Breast or chest wall only	51 (6%)	60 (7%)
Breast or chest wall plus regional lymph nodes	698 (87%)	789 (87%)
Regional lymph nodes only	5 (1%)	11 (1%)
Missing	2 (<1%)	2 (<1%)

Data are n (%), mean (SD), or median (IQR). Percentages might add up to more than 100% due to rounding.
*Ten patients (five in each group) terminating trial participation before their 1-year follow-up visit, at which adjuvant treatment was reported, are excluded. †31 patients did not receive endocrine treatment due to patient wish (n=13), depression (n=1), severe body pain (n=1), and unregistered reasons (n=16).

Table 1: **Clinical characteristics of SENOMAC patients included in current analysis (N=1705)**

than the cALND group; however, there was no difference for the domains of social activities and household activities (table 2). Severe or very severe impairment of physical arm function was significantly more common after cALND (84 [13%] of 634) than after sentinel lymph node biopsy alone (30 [4%] of 708; p<0·0001), with an absolute risk increase of 9%. The number needed to harm was thus 11 (ie, 1 divided by 0·09); such that 11 patients undergoing cALND resulted in one patient with severe or very severe impairment of physical arm function.

	Completion axillary lymph node dissection group (n=634)	Sentinel lymph node biopsy alone group (n=708)	p value
Physical function			
Mean score	21·9 (21·6)	12·1 (16·1)	<0·0001
No or a small problem	416 (66%)	599 (985%)	<0·0001
Moderate problem	132 (21%)	72 (10%)	..
Severe or very severe problem	84 (13%)	30 (4%)	..
Missing	2 (<1%)	7 (1%)	..
Mental function			
Mean score	13·9 (21·0)	8·3 (16·5)	<0·0001
No or a small problem	503 (79%)	634 (90%)	<0·0001
Moderate problem	71 (11%)	28 (4%)	..
Severe or very severe problem	54 (9%)	32 (5%)	..
Missing	6 (1%)	14 (2%)	..
Household activities			
Mean score	17·0 (21·5)	13·2 (20·2)	0·0011
No or a small problem	472 (74%)	564 (80%)	0·039
Moderate problem	91 (14%)	76 (11%)	..
Severe or very severe problem	63 (10%)	55 (8%)	..
Missing	8 (1%)	13 (2%)	..
Mobility activities			
Mean score	22·4 (21·1)	17·7 (19·3)	<0·0001
No or a small problem	397 (63%)	509 (72%)	0·0023
Moderate problem	146 (23%)	130 (18%)	..
Severe or very severe problem	80 (13%)	63 (9%)	..
Missing	11 (2%)	6 (1%)	..
Social activities			
Mean score	15·8 (19·8)	13·4 (18·2)	0·024
No or a small problem	465 (73%)	564 (80%)	0·053
Moderate problem	110 (17%)	93 (13%)	..
Severe or very severe problem	44 (7%)	44 (6%)	..
Missing	15 (2%)	7 (1%)	..
Total score			
Mean score	19·1 (18·2)	13·2 (14·9)	<0·0001
No or a small problem	448 (71%)	586 (83%)	<0·0001
Moderate problem	139 (22%)	94 (13%)	..
Severe or very severe problem	47 (7%)	28 (4%)	..

Data are mean (SD) scores and n (%) for each category. Mean scores per category were compared between groups using Student's *t* test, and distribution of participants across functioning categories was compared with the χ^2 test. Lymph-ICF questionnaire=Lymphedema Functioning, Disability, and Health Questionnaire.

Table 2: **Patient-reported arm function using the Lymph-ICF questionnaire, 1 year after randomisation, in the responding population (n=1342)**

Five (1%) of 903 patients in the sentinel lymph node biopsy alone and 101 (13%) of 802 patients in the cALND group had four or more nodal metastases, an absolute difference of 12%. In the sentinel lymph node biopsy alone group, four or more nodal metastases were detected on unintentional removal of additional non-sentinel lymph nodes without a regular cALND. The number needed to diagnose was 8 (ie, 1 divided by 0·12); such that eight patients needed to undergo a cALND to identify one candidate for adjuvant abemaciclib in accordance with monarchE criteria. The published 5-year invasive disease-free survival rates from cohort 1 in the monarchE trial are 83·2% (95% CI 81·5–84·7) in the abemaciclib plus endocrine therapy group and 75·3% (95% CI 73·4–77·2) in the endocrine therapy alone group, resulting in an absolute risk reduction of 7·9%.[6,7] The number needed to treat is thus 13 (1 divided by 0·079); 13 patients need to be treated with abemaciclib to avoid one invasive disease-free survival event at 5 years. This finding implies that 104 (8 multiplied by 13) patients would need to undergo a cALND to avoid one invasive disease-free survival event at 5 years.

The AMAROS trial reported clinical signs of lymphoedema after 5 years in 24·5% in the cALND group versus 11·9% in the axillary radiotherapy group (absolute risk increase of 12·6%). The corresponding figures for treatment for arm lymphoedema at any timepoint up to 5 years were 36·0% versus 20·2% (absolute risk increase of 15·8%). Thus, the number needed to harm for clinical signs of lymphoedema was eight and for treatment of lymphoedema was 6 (1 divided by 0·126 and 0·158, respectively).

This finding implies that if using cALND as a staging tool, nine patients (104 divided by 11) would develop severe or very severe impairment of physical arm function, 13 patients (104 divided by 8) would develop clinical signs of lymphoedema, and 17 patients (104 divided by 6) would need lymphoedema treatment, to avoid one invasive disease-free survival event at 5 years if completing 2 years of adjuvant abemaciclib.

Discussion

In this analysis, we evaluated the potential consequences of cALND in patients whose indication for adjuvant abemaciclib solely depends on the diagnosis of pN2–3 status. We determined that 104 patients would need a cALND to avoid one invasive disease-free survival event at 5 years by receiving 2 years of adjuvant abemaciclib and that nine patients would develop severe or very severe impairment of physical arm function to avoid one invasive disease-free survival event at 5 years. Although adjuvant abemaciclib has become standard of care in high-risk luminal breast cancer,[7,9,20] it has not yet shown an overall survival benefit.[6,7] And so, in light of these findings, which are in line with previous contributions to this clinical debate,[10,11,21] we discourage the use of cALND in this setting.

To date, the monarchE trial has reported data up to a median follow-up of 54 months and, considering that luminal breast cancer can recur late in the disease course, a treatment effect of abemaciclib on overall survival might still be found. However, an invasive disease-free survival benefit does not necessarily translate into an overall survival benefit.[22] In subgroup analyses of the monarchE trial, patients aged 65 years and older, those with stage IIB breast cancer, and those with tumours of Nottingham histological grade 1 had no significant benefit of treatment with abemaciclib regarding invasive disease-free survival at a median follow-up of 42 months (IQR 37–47).[6] Hence, in the subpopulation of SENOMAC used in the current analysis, of whom 691 (40·5%) of 1705 had stage IIB breast cancer (in this case, T2N1), 432 (25%) had grade 1 tumours, and 725 (43%) were aged 65 years or older, all would have gained little, if any, benefit from adjuvant abemaciclib. Importantly, abemaciclib has a substantially higher risk of grade 3 or worse adverse events than does endocrine treatment alone.[6,7] Although two treatment-related deaths were reported in the abemaciclib plus endocrine treatment group in monarchE, none occurred in the endocrine treatment alone group.[6] In the abemaciclib plus endocrine treatment group, 180 (6·4%) of 2791 patients discontinued both treatments due to adverse events, while abemaciclib treatment interruption due to adverse events occurred in 1721 (61·7%) of 2791 patients.[6] To add the toxicity of cALND to this burden, without the promise of a survival benefit, appears inappropriate.

The here-selected patient population of the SENOMAC trial would have no indication for adjuvant abemaciclib if they had not been found to have pN2–3 status via cALND. Thus, the breast cancer risk profile of the selected patient population is probably lower than in the monarchE population. Recently published results from the NATALEE trial,[8] where cALND was not required to identify patients with an indication for ribociclib treatment, might alter the landscape of adjuvant CDK4/6 inhibitors via its broader inclusion criteria.[8] However, these more broad eligibility criteria might also increase the number of patients receiving the treatment without gaining any survival benefit.

Several trials have confirmed the non-inferiority of the omission of cALND compared with sentinel lymph node biopsy alone with or without nodal radiotherapy. ACOSOG Z0011 and AMAROS reported equivalent 10-year overall survival rates in 2017 and 2022.[1,2] However, because these trials, as well as the SENOMAC trial, preceded the approval of abemaciclib by the FDA in October, 2021,[23] and by the European Medicines Agency in April, 2022,[24] abemaciclib was not given to patients in these trials. Therefore, a potential survival effect of abemaciclib in the group that received cALND in the SENOMAC, Z0011, and AMAROS trials could not be evaluated. The proportion of patients with pN2–3 status in the cALND groups was 13·7% in ACOSOG Z0011[2] and 12·9% in AMAROS,[1] which is in line with patients in SENOMAC who received primary surgery (12·9%).[5,25] However, no information on the number of patients with grade 3 tumours among these patients in Z0011 and AMAROS is available, which would present an indication for abemaciclib independent of cALND.

A previous analysis of patient-reported outcome measures from Swedish and Danish participants in SENOMAC showed significantly more arm morbidity 1 year after cALND than after sentinel lymph node biopsy only.[13] In the current analysis, updated patient-reported outcome measures on the here-selected trial population with a good questionnaire response rate confirm these findings. Interestingly, although the AMAROS trial showed an approximately two-times higher risk of lymphoedema after cALND than after axillary radiotherapy at 1 year, 3 years, and 5 years of follow-up,[1] patient-reported arm symptoms did not significantly differ between groups at most of these timepoints.[1] This finding might be due to differences in adjuvant radiotherapy. In SENOMAC, axillary nodal volumes were irradiated in most patients after cALND, whereas participants in AMAROS received axillary radiotherapy after cALND only in case of high nodal burden.[1,5] Because reported arm symptoms and signs of lymphoedema persisted throughout follow-up in the AMAROS trial, focusing on preventive measures (eg, restricting the use of cALND) to reduce the risk for severe arm morbidity is important.

Our analysis has some limitations. The analysis evaluating consequences of cALND in the context of the monarchE trial was not prespecified; however, the analysis of 1 year patient-reported outcome measures was prespecified in the study protocol and statistical analysis plan. Patient-reported outcome measures were not adjusted for baseline data because they were first collected after randomisation as an early postoperative measurement and, thus, a true baseline measure is absent. However, given the randomised design of the SENOMAC trial and the large trial population, baseline arm morbidity should not differ significantly between groups, and the absence of adjustment for baseline should not impair the reliability of our 1-year results. Another limitation is that arm morbidity was exclusively measured through patient-reported outcome measures collected by questionnaire because objective measurements of arm volume, circumference, and range of motion were not part of the study protocol. Patient-reported outcome measures without objective measurements might restrict the capture of actual lymphoedema and restricted range of motion and do not always align with objective measures. Nevertheless, patient-reported outcome measures might better reflect the patient-experienced burden than clinician-reported measures.[26] Therefore, 5-year arm lymphoedema outcomes reported in the AMAROS trial[1] were also considered. Although

numbers needed to treat, diagnose, and harm do not consider patients' baseline risk, they are point estimates that are commonly given without a confidence interval. The absence of a baseline measurement should not be considered a limitation, especially considering that only data from randomised trials were used in this analysis. Thus, our findings offer a simplified but pragmatic clinical illustration of benefit or harm with a robustness that is supported by the high number of patients included in the analysis. Finally, the number needed to treat could only be based on cohort 1 of the monarchE trial, which also includes patients with grade 3 and T3 tumours. Because these patients were not included in the SENOMAC subpopulation evaluated here, the monarchE cohort 1 should be regarded as a higher risk population, indicating that the number needed to treat applicable to the SENOMAC subpopulation might be even higher than that calculated here.

Contributors

JdB had the overall responsibility for study design and performance, funding, data collection, interpretation of data, and writing of the manuscript. RS did the statistical analysis. JdB and RS directly accessed and verified the underlying raw data reported in the manuscript. All authors contributed to study design and data collection, resources, data curation and project administration, had full access to the data in the study, critically evaluated and commented on the content of the manuscript, and assumed final responsibility for the decision to submit for publication.

Declaration of interests

JdB declares honoraria for educational event lectures for AstraZeneca, Novartis, and Pfizer. ODG declares honoraria for lectures and presentations from MSD, AstraZeneca, Eli Lilly, Becton, Dickinson and Company, and Bayer and the participation on a data safety monitoring or advisory board for MSD. MS is chairwoman for the Research Committee at the Swedish Cancer Society. All other authors declare no competing interests.

Data sharing

De-identified participant data can be made available upon reasonable request and with the appropriate approvals of relevant Ethical Review Authorities once the primary endpoint has been published. Proposals should be directed to the corresponding author at jana.de-boniface@ki.se; to gain access, data requestors will need to sign a data access agreement. The study protocol and statistical analysis plan are available upon request at any time.

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