



SEOM-GEICAM-SOLTI clinical guidelines for early-stage breast cancer (UPDATE 2025)

Francisco Ayala de la Peña¹ · Silvia Antolín Novoa² · Joaquín Gavilá Gregori³ · Lucía González Cortijo⁴ · Fernando Henao Carrasco⁵ · María Teresa Martínez Martínez⁶ · Cristina Morales Estévez⁷ · Agostina Stradella⁸ · María Jesús Vidal Losada⁹ · Eva Ciruelos^{10,11}

Received: 5 November 2025 / Accepted: 9 November 2025 / Published online: 29 November 2025
© The Author(s) 2025

Abstract

Breast cancer is the leading cause of cancer in women in Spain and its annual incidence is rapidly increasing. As a result of the screening programs in place, nearly 90% of breast cancer cases are detected in early and potentially curable stages. In recent years, locoregional and systemic therapies have increasingly been directed by new diagnostic tools that have improved the balance between toxicity and clinical benefit. New therapeutic strategies, such as immunotherapy, targeted drugs, and antibody–drug conjugates, have also improved outcomes in some patient subgroups. This clinical practice guideline for early-stage breast cancer (updated in 2025) is based on a systematic review of relevant studies and on the consensus of experts from the Spanish Breast Cancer Research Group (GEICAM), Spanish Collaborative Group for the Study, Treatment and Other Experimental Strategies in Solid Tumors (SOLTI), and Spanish Society of Medical Oncology (SEOM).

Keywords Adjuvant · Early breast cancer · Follow-up · Neoadjuvant

✉ Francisco Ayala de la Peña
frayala@ucm.es

Silvia Antolín Novoa
Silvia.antolin.novoa@sergas.es

Joaquín Gavilá Gregori
jogagre@hotmail.com

Lucía González Cortijo
lucia.gonzalezc@quironsalud.es

Fernando Henao Carrasco
ferheca@gmail.com

María Teresa Martínez Martínez
maitemartinez3@yahoo.es

Cristina Morales Estévez
cristinamoralessesevez@gmail.com

Agostina Stradella
astradella@iconcologia.net

María Jesús Vidal Losada
Mjvidal@clinic.cat

Eva Ciruelos
eva.ciruelos@gmail.com

¹ Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Hospital Oncológico y de Terapias Avanzadas, Calle Maiquez 7, 28007 Madrid, Spain

² Department of Medical Oncology, Complejo Hospitalario Universitario, A Coruña (CHUAC), Coruña, Spain

³ Fundación Instituto Valenciano de Oncología (IVO), Valencia, Spain

⁴ Medical Oncology Department, Hospital Universitario Quirónsalud, Madrid, Spain

⁵ Hospital Universitario Virgen Macarena, Seville, Spain

⁶ Medical Oncology Department, INCLIVA Biomedical Research Institute, Hospital Clínico of Valencia, University of Valencia, Valencia, Spain

⁷ Hospital Universitario Reina Sofía, Córdoba, Spain

⁸ Medical Oncology Department, Institut Català d'Oncologia L'Hospitalet, Barcelona, Spain

⁹ Hospital Clínic, Barcelona, Spain

¹⁰ Medical Oncology Department, Breast Cancer Unit, University Hospital 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain

¹¹ HM Hospitales, Madrid, Spain

Introduction

Breast cancer is a major public health problem, given its high incidence, prevalence, and mortality. In Spain, it is the most common cancer among women, accounting for 35,000 new cases per year, and the leading cause of cancer-related mortality in the female population, responsible for 6572 deaths in 2020 [1].

Breast cancer has marked clinical and biological heterogeneity. Therefore, many therapeutic decisions are individualized on the basis of molecular and clinical characteristics. Despite the success in implementing early detection campaigns, up to one in three patients will develop metastases. Moreover, approximately one in 8–9 new diagnoses currently present as metastatic disease; these figures may be worse because of screening delays across the country due to the COVID-19 pandemic [2].

The aim of these guidelines is to summarize and categorize current evidence that forms the basis of therapeutic recommendations for the clinical management of early-stage breast cancer.

Methodology

This guideline is based on a systematic review of published studies and a consensus of ten oncologists who specialize in breast cancer treatment from the Spanish Breast Cancer Research Group (GEICAM), the Spanish Collaborative Group for the Study, Treatment and Other Experimental Strategies in Solid Tumors (SOLTI), and the Spanish Society of Medical Oncology (SEOM), plus an external review panel comprising two experts designated by SEOM. Levels of evidence and grades of recommendation assigned were based, with modifications, on the Infectious Diseases Society of America-US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines [3] (Supplementary Table S1).

The updated recommendations in these guidelines (July 2025) reflect the results of clinical trials released since the publication of the original guidelines (2022), and minor amendments to the wording of the original guidelines. The updated version of the guidelines has been approved by all the authors. The new recommendations (versus those provided in the 2022 guidelines) are shown in Table 1.

Diagnosis and staging

To diagnose breast cancer, a clinical, radiological, and pathological examination is necessary. Staging should be conducted according to the tumor/node/metastasis (TNM) staging system and the American Joint Commission of

Cancer (AJCC) system [4]. A full personal and family history, and a complete physical examination (palpation of the breasts, regional lymph nodes, and assessment for distant metastases) should be performed.

Radiological tests are essential to establish an accurate diagnosis. Bilateral mammography and ultrasound of the breast and regional lymph nodes (I, A) [5] form the basis of a diagnostic assessment. New techniques, such as 3-dimensional (3D) mammography or 3D ultrasound, increase diagnostic accuracy but are not routinely implemented. Core needle biopsy (preferably under ultrasound or stereotactic guidance) (I, A), and fine needle aspiration or core biopsy of suspicious lymph nodes (II, A) are recommended. Breast magnetic resonance imaging (MRI) is optional (I, B) and should only be considered in cases of positive axillary nodes, occult primary breast cancer, Paget's disease of the nipple, lobular carcinoma, and multifocal, multicentric lesions, and in patients with breast implants. Breast MRI is also recommended pre- and post-neoadjuvant treatment to define the extent of disease and monitor treatment response (III, A) [6].

Additional tests include: (i) evaluation of cardiac function, which is imperative when using anthracyclines or anti-human epidermal growth factor receptor 2 (HER2)-targeted therapies (I, A) [7]; (ii) laboratory tests (complete blood count, liver and renal function, alkaline phosphatase, and calcium), which can be routinely performed but do not appear to improve detection of occult metastatic disease (III, C) [8]; and (iii) additional systemic staging, which should be contemplated when disease is detected in stage III or when signs, symptoms, or laboratory values indicate possible metastasis; this more comprehensive study should include chest, abdominal, and pelvic imaging, and bone scan (III, B). Position emission tomography/computed tomography may be of use when traditional imaging tests are inconclusive (III, A), or in cases of locally-advanced tumors [9].

Pathology and molecular biology

The pathological diagnosis should be made according to the World Health Organization (WHO) classification. The two most frequent breast cancer subtypes are invasive carcinoma of no special type, which accounts for approximately 70–75% of cases, and lobular carcinoma, representing between 12–15% of all breast cancers; the other $\leq 5\%$ are rare histologies, each with distinct pathologic features and prognosis [10, 11]. Tumor grade and the presence of in situ carcinoma are also relevant features to determine.

Estrogen receptor (ER) and progesterone receptor (PgR) expression should be ascertained by immunohistochemistry, and reporting of the new category of ER-low positive should be done for tumors with 1–10% positive staining [12].

Table 1 Summary of changes made in the 2025 guidelines**Methodology (Supplementary Table S1)**

The definitions of the grades of recommendation and evidence have been reworded, and two further lower levels of quality of evidence (IV and V) have been added

Local–regional therapy, surgery

The grade of recommendation and quality of evidence for the use of ink in the tumor to indicate a sufficient surgical margin has been downgraded (to II, A), and the patient group refined (patients with invasive breast cancer or ductal carcinoma in situ associated with invasive breast carcinoma)

A recommendation has been added for the appropriate surgical margin in patients with pure ductal carcinoma in situ (II, A)

The recommendation for sentinel lymph node biopsy in patients undergoing BCS with clinically negative axilla assessed by ultrasound imaging has been qualified on the basis of the SOUND and INSEMA trials (may be omitted in postmenopausal patients with grade 1–2 HR-positive, HER2-negative cT1N0 tumors without lymphovascular invasion undergoing BCS after multidisciplinary evaluation of the adjuvant plan) [I, B]

A recommendation has been added to indicate that axillary lymph node dissection should be omitted in patients with one or two positive lymph nodes post-BCS for pT1–T2 tumors if adjuvant systemic therapy and breast irradiation are planned (I, A)

The origin of the data on which the recommendation for axillary lymph node dissection is based has been clarified (the SENOMAC trial) and the size/extent of tumors related to mastectomy has been defined (T1-3)

Prognostic gene expression–based assays and dynamic biomarkers

The quality of evidence for the use of Prosigna[®] in postmenopausal patients with node-negative tumors has been upgraded (to II, A)

A recommendation has been added regarding the use of dynamic changes in Ki67 for prognostic stratification to determine the expected benefit of adjuvant chemotherapy after preoperative ovarian function suppression and an aromatase inhibitor in premenopausal patients with a recurrence score of 0–25 (II, C)

Systemic treatment for early-stage luminal-type breast cancer, adjuvant endocrine therapy, postmenopausal patients

The patient group in whom bisphosphonates are recommended has been refined and expanded (women who are postmenopausal, undergoing ovarian suppression at high risk of recurrence, and those with treatment-related bone loss)

MAF test is added as an option to identify patients who would not add adjuvant bisphosphonates in their adjuvant hormone treatment (III, B)

Data on which the recommendation to use adjuvant abemaciclib is based have been updated (5-year absolute invasive disease-free survival benefit from the monarchE trial), and the restriction on Ki67 levels removed

A recommendation has been added for the use of adjuvant ribociclib in high- and intermediate-risk patients (I, B)

Figure 1 has been updated to reflect the new/amended recommendations

Systemic treatment for early-stage luminal-type breast cancer, Adjuvant chemotherapy in hormone receptor-positive disease

The patient group in which to use dose-dense schedules of anthracycline-based regimens (with granulocyte colony-stimulating factor support) has been expanded (to include most patients)

A recommendation has been added for the use of anti-Müllerian hormone levels to predict the benefit of adjuvant chemotherapy in premenopausal patients aged approximately 55 years and/or of uncertain menopausal status (II, C)

The data on which the recommendation to use adjuvant olaparib in HR-positive, HER2-negative patients carrying a germline pathogenic variant in *BRCA1/2* with high-risk features was based has been updated (the OlympiA trial)

Systemic treatment for HER2-positive early-stage breast cancer, neoadjuvant treatment

Patients in whom the HER2DX 27 gene test could be used has been refined (use in patients with HER2-positive tumors who plan to undergo neoadjuvant systemic therapy)

Systemic treatment for HER2-positive early-stage breast cancer, adjuvant treatment

The recommendation regarding dual trastuzumab plus pertuzumab in the high-risk node-positive population has been upgraded (I, A)

The data on which the recommendation to use adjuvant trastuzumab emtansine was based have been updated (the KATHERINE study)

Systemic treatment for triple-negative breast cancer, neoadjuvant treatment

A recommendation has been added to indicate that neoadjuvant systemic therapy is the preferred approach for cT1c-4 N0 or N-positive disease (I, A)

The recommendation to add platinum compounds to standard sequential anthracycline and taxane regimens has been strengthened (to I, A)

The data on which the recommendation to use pembrolizumab was based have been updated (the KEYNOTE-522 study), and the recommendation to use pembrolizumab has been strengthened (to I, A)

A recommendation has been added to use chemotherapy without pembrolizumab in triple-negative cT1cN0 tumors treated with neoadjuvant systemic therapy (I, A)

The recommendation to use adjuvant olaparib has been strengthened (to I, A) based on the updated results of the OlympiA trial

A recommendation has been added regarding adjuvant combined or sequential use of pembrolizumab with either capecitabine or olaparib (III, C)

Figure 3 has been updated

Table 1 (continued)

BSC breast-conserving surgery, *cN* clinically positive axillary node, *cT* clinical tumor stage, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *N* node

HER2 status should be determined as per American Society of Clinical Oncology–College of American Pathologists (ASCO-CAP) guidelines (I, A) [13]. Proliferation markers such as Ki67 yield additional useful information; nevertheless, the high inter-observer variability in Ki67 determination must be taken into consideration when using this marker for decision-making [14].

Recent years have witnessed the emergence of new markers aimed at substantiating differences in pathogenesis, treatment response, and prognosis. Tumor-infiltrating lymphocytes (TILs) have proven to predict pathologic complete response (pCR) to chemotherapy (CT) and good prognosis in triple-negative breast cancer (TNBC) and HER2-positive breast cancer [15, 16].

In the early, hormone receptor (HR)-positive, HER2-negative setting, various platforms are available (Oncotype®, MammaPrint®, Prosigna® and EndoPredict®) and they can be of value for determining adjuvant treatment in pre- or post-menopausal patients with node-negative disease and in post-menopausal patients with 1–3 positive lymph nodes [17–19].

In HER2-positive disease, the HER2DX 27-gene test has recently emerged as a useful clinical tool [20–23]. This test provides two independent scores indicating prognosis when disease has been treated with trastuzumab-based CT (HER2DX risk-score), and the probability of achieving a pCR following trastuzumab-based therapy (HER2DX pCR-score).

Local-regional therapy

Surgery

Surgical treatment of breast cancer may consist of tumor excision with removal of some surrounding normal breast tissue (i.e. breast conserving surgery [BCS]) or mastectomy [24]. Long-term follow-up of randomized clinical trials has revealed similar survival rates for women treated with either BCS or mastectomy [25]. Mastectomy is indicated in the following cases: locally advanced tumors, tumor multicentricity, small breast size for tumor volume, inability to achieve negative surgical margins after multiple resections, and contraindications to radiotherapy (RT) (I, A) [26, 27].

Currently, an increasing percentage of women with stage II or III breast cancer receive primary neoadjuvant systemic therapy (NST). In these patients, surgical and radiation treatments are based on the tumor's initial stage and response to

NST. The absence of ink in the tumor indicates a sufficient surgical margin in most cases of invasive breast cancer or ductal carcinoma in situ associated with invasive breast carcinoma (II, A). In pure ductal carcinoma in situ, the absence of ink in the tumor is not considered a sufficient surgical margin; at least a 2 mm margin is recommended in these cases (II, A) [28].

Patients with breast cancer and germline *BRCA1/2* mutations can be considered for BCS, with local control similar to that of non-carriers of these mutations (I, A). The increased risk of contralateral breast cancer and of new cancers in the ipsilateral breast warrant discussing bilateral mastectomy with the patient (I, A). Nipple-sparing mastectomy is a reasonable approach in these women, provided there is adequate distance from the tumor surgical margin [29].

Sentinel lymph node biopsy (SLNB) is standard for patients undergoing BCS with clinically negative axilla assessed by ultrasound imaging (I, A) [30], although, according to the SOUND [31] and INSEMA [32] trials, it may be omitted in postmenopausal patients with grade 1–2 HR-positive, HER2-negative cT1N0 tumors without lymphovascular invasion undergoing BCS after multidisciplinary evaluation of the adjuvant plan (I, B). Axillary lymph node dissection (ALND) should be omitted after SLNB in patients with one or two positive lymph nodes post-BCS for pT1–T2 tumors if adjuvant systemic therapy and breast irradiation are planned (I, A). According to the SENOMAC trial, ALND should also be omitted after SLNB with one or two positive lymph nodes following mastectomy of T1–3 tumors, provided that regional nodal irradiation (RNI), including the axilla, is planned (I, A) [33]. In women undergoing mastectomy with positive sentinel lymph nodes for whom radiation is not planned, complete axillary dissection is recommended (III, B) [28, 34].

Clinically node-positive patients after NST are advised to undergo complete axillary dissection (I, A). SLNB is a post-NST staging procedure for cN0 patients (I, A). In those with a clinically positive axillary node (cN1) who achieve a complete clinical response after NST, axillary dissection can be avoided if ≥ 3 sentinel nodes are identified and all are negative, or when the marked involved node(s) at diagnoses is/are removed, in addition to the sentinel node, and all of them are free of tumor cells (II, B) [35]. Any residual nodal disease (except for isolated tumor cells, which are not considered as residual disease) after NST on sentinel node biopsy usually warrants ALND (RT vs surgery trials are ongoing) (I, A). Patients with cN2–N3 axillary disease should

Table 2 Types of prognostic gene expression-based assays

Platform	Description	Validated	Site	Technology	Risk classification	Prospective randomized study	Evidence
Oncotype DX [®]	21-gene signature	N0 (prem and postm) N1 (postm)	Central	Microarray	Recurrence score low, intermediate, high	TAILORx (Sparano 2018) RxPONDER (Kalinsky 2021)	I, A
MammaPrint [®]	70-gene signature Tumoral subtype Blue Print (luminal, basal, ERBB2)	N0 N1 (postm)	Central	RT-qPCR	Ultralow, low, high	MINDACT (Car-doso 2016)	I, A
EndoPredict [®]	11-gene signature	N0 N1 (postm)	Local labs	RT-qPCR	Low, high EPclin risk score	None	II, B
Prosigna [®]	50-gene signature Tumoral subtype (luminal A, B, HER2-enriched, basal-like)	N0 (postm)	Local labs	nCounter (direct mRNA counting)	Low, intermediate, high risk of recurrence Intrinsic subtypes (15–19)	OPTIMA (ongo-ing)	II, A

EPclin EndoPredict and clinical combined score, *ERBB2* erythroblastic oncogene B 2, *HER2* human epidermal growth factor receptor 2, *labs* laboratories, *N* node, *postm* postmenopausal, *prem* premenopausal, *RT-qPCR* reverse transcription quantitative real-time polymerase chain reaction

undergo ALND, regardless of response to NST (I, A) [28, 36, 37].

Adjuvant radiotherapy

After BCS, adjuvant RT is the standard treatment (I, A) [38, 39]. Hypofractionated whole breast irradiation (WBI) represents the preferred approach, with a treatment duration of 1–4 weeks (I, A). Five-fraction WBI regimens have also emerged as standard of care for certain patients based on data from the FAST and FAST-Forward trials (I, A) [40, 41]. Omission of breast irradiation in elderly patients with low-risk ER-positive tumors is considered a safe option, although a higher incidence of local recurrence is expected (I, A) [42].

In cases of involvement of ≥ 4 axillary lymph nodes, RNI is recommended, as it increases survival in node-positive breast cancer (I, A) [43]. In cases of 1–3 positive lymph nodes, if there are adverse prognostic factors, such as triple negativity or HER2 positivity, luminal B cancers, and in women with residual disease after NST, experts recommend RNI, regardless of whether mastectomy or BCS have been performed (I, B). Similarly, postmastectomy RT to the chest wall and regional lymph nodes is recommended in cases of ≥ 4 positive nodes (I, A).

Principles of adjuvant systemic therapy

Breast cancer is a heterogeneous disease, with different subtypes having distinct biological, molecular, and clinical outcomes. Systemic adjuvant treatment is commonly used in

early breast cancer with the intention of lowering the rate of locoregional or systemic relapses and death from the disease. Treatment decisions are based on clinical (age, comorbidities) and pathologic factors (tumor size, nodal status, grade, Ki67, HR status, and HER2 status). Multigenic tests provide information beyond standard clinical and pathologic prognostic factors that can aid in making treatment decisions.

Prognostic gene expression-based assays and dynamic biomarkers

Gene expression-based assays, such as the Oncotype DX[®] Recurrence Score, MammaPrint[®], EndoPredict[®], and Prosigna[®], can be used to gain additional prognostic and/or predictive information regarding the benefit of adjuvant CT in early HR-positive and HER2-negative breast cancer (I, A) (Table 2). Data have been reported to inform adjuvant endocrine therapy (ET) and CT use on the basis of patient age, menopausal status, and number of axillary nodes involved (II, B) [19, 44–51] (Tables 2 and 3).

Genomic platforms are not recommended for the following: clinically low-risk tumors (pT1a, b, node-negative, low-grade, ER-high) and/or patients with health conditions who are not candidates for CT or who do not desire CT (I, D). Genomic platforms are also not recommended for the following: 1–3 involved nodes coexisting with other high-risk factors in most premenopausal patients, or patients with > 3 positive nodes for whom adjuvant CT is indicated (I, D).

Table 3 SEOM clinical practice guidelines for early breast cancer (2025): Summary of recommendations

Recommendation	Category, grade
Diagnosis and initial workup	
Bilateral mammography and ultrasound of breast and regional lymph nodes in patients with suspected breast cancer	I, A
Core needle biopsy (preferably under ultrasound or stereotactic guidance) in patients with suspected breast cancer	I, A
Fine needle aspiration or core biopsy of suspicious lymph nodes	II, A
Immunohistochemical evaluation of ER and PgR together with HER2 expression (following ASCO-CAP guidelines) should be performed in the breast biopsy	I, A
Bilateral breast MRI, with histologic confirmation of additional findings, as part of initial staging in cases of positive axillary nodes; occult primary breast cancer; Paget's disease of the nipple; lobular carcinoma; multifocal, multicentric lesions; and breast implants	I, B
Bilateral breast MRI is recommended before and after neoadjuvant treatment to define the extent of disease and monitor response to treatment	III, A
Laboratory testing as part of initial staging of patients with confirmed breast cancer	III, C
Additional staging with chest and abdomen-pelvis computed tomography and bone scan in patients with stage III disease and/or with clinical or laboratory findings suggestive of metastases	III, B
Staging positron emission tomography /computed tomography can be of use when traditional imaging test are equivocal	III, A
Evaluation of cardiac function in patients requiring anthracyclines and/or anti-HER2 targeted therapy	I, A
Surgery	
Consideration of BCS as first surgical option in stages I–II. Mastectomy is indicated in cases of locally advanced cancer, tumor multi-centricity, small breast size for tumor volume, inability to achieve negative surgical margins after multiple resections, and contraindications to radiotherapy	I, A
No indication of additional excision in patients with no ink on invasive tumor or DCIS with invasive breast carcinoma after BCS	II, A
In pure DCIS, the absence of ink in the tumor is not considered a sufficient surgical margin; at least a 2 mm margin is recommended in these cases	II, A
Patients with breast cancer and germline <i>BRCA1/2</i> mutations can be considered for BCS, with local control rates similar to those of non-carriers of these mutations	I, A
Bilateral mastectomy should be offered as part of an appropriate counseling process in <i>BRCA1/2</i> mutation carriers	I, A
SLN biopsy is standard in patients with clinically negative axillary nodes	I, A
SLN biopsy may be omitted in postmenopausal patients with grade 1–2 HR-positive, HER2-negative cT1N0 tumors without LVI undergoing BCS, provided that a multidisciplinary assessment of the impact of SLN biopsy omission in the entire adjuvant plan has been done	I, B
ALND should be omitted in patients with stage I–II disease and <3 positive axillary nodes after SLN biopsy and lumpectomy followed by adjuvant systemic therapy and radiotherapy	I, A
ALND should be omitted in patients with T1–3 tumors and <3 three positive axillary nodes after SLN biopsy and mastectomy, provided that adjuvant systemic therapy and regional nodal irradiation including the axilla are indicated	I, A
ALND is recommended in patients with positive axillary nodes and mastectomy for whom irradiation is not planned	III, B
In patients with cN0 tumors, SLN biopsy is the standard axillary staging procedure after NST	I, A
In patients with cN1 receiving NST, ALND might be avoided in patients with downstaging of axilla to clinically negative if ≥ 3 sentinel nodes are identified and all of them are negative, or when the involved node(s) marked at diagnoses is/are removed as well as the sentinel node and all are free of tumor cells	II, B
In patients receiving NST, ALND should be performed in women with any residual disease on sentinel node biopsy	I, A
In patients with cN2–3 tumors receiving NST, ALND should be performed regardless of response to NST	I, A
Adjuvant radiotherapy	
Adjuvant radiation therapy is the standard treatment after BCS	I, A
Hypofractionated schemes are preferred for external beam whole radiation therapy after BCS	I, A
Breast irradiation may be safely omitted after BCS in elderly patients with low risk ER-positive tumors, assuming a higher rate of local recurrence	I, A
Regional nodal irradiation should be administered in patients with ≥ 4 involved nodes after BCS or mastectomy	I, A
Regional nodal irradiation is recommended in patients with 1–3 involved nodes after BCS or mastectomy in cases with adverse prognostic factors (e.g. triple negativity, HER2 positivity, luminal B cancers)	I, B
Regional nodal irradiation is recommended in patients with residual nodal disease after NST and BCS or mastectomy	I, B
Postmastectomy radiation therapy to the chest wall and regional node irradiation should be administered in patients with ≥ 4 involved nodes	I, A

Table 3 (continued)

Recommendation	Category, grade
Prognostic gene expression–based assays and dynamic biomarkers to guide systemic adjuvant treatment for HR-positive HER2-negative breast cancer	
In HR-positive and HER2-negative breast cancer, genomic platforms are not recommended in clinically low-risk patients (pT1a-b, N0, low-grade, ER-high) and/or in patients who are not eligible for, or who do not desire, CT	I, D
In HR-positive and HER2-negative breast cancer, genomic platforms are not recommended in: patients with 1–3 involved nodes coexisting with other high-risk factors, or in patients with > 3 positive nodes for whom adjuvant CT is indicated	I, D
Oncotype DX® is recommended in premenopausal patients with node-negative tumors to predict benefit from adjuvant CT	I, A
Oncotype DX® and MammaPrint® may be used to guide adjuvant treatment in postmenopausal or > 50-year-old patients with node-negative disease or 1–3 positive nodes	I, A
EndoPredict® may be used to guide adjuvant treatment in postmenopausal or > 50-year-old patients with node-negative disease or 1–3 positive nodes	II, B
Prosigna® may be used in postmenopausal patients with node-negative tumors	II, A
Dynamic changes of Ki67 after 2 weeks of preoperative ET in postmenopausal women may be considered as a surrogate prognostic factor	II, B
Dynamic changes in Ki67 after 4 weeks of preoperative OFS and an AI in premenopausal patients with a recurrence score of 0–25 might provide further prognostic stratification to determine the expected benefit of adjuvant CT	II, C
Adjuvant and neoadjuvant systemic treatment of luminal breast cancer	
Adjuvant therapy should be started < 12 weeks after surgery	I, A
Adjuvant ET should be offered to any patient with HR-positive disease (ER or PgR, if either or both are positive, defined as ER ≥ 1% and/or PgR > 10%), regardless of other prognostic factors	I, A
Recommendations for endocrine therapy in premenopausal patients	
Adjuvant ET with tamoxifen for 5 years is recommended as a standard treatment for low-risk premenopausal women with HR-positive breast cancer	I, A
Extended adjuvant ET with tamoxifen for up to 10 years should be considered in higher-risk patients who remain premenopausal during the entire adjuvant period	I, B
OFS for 2 to 5 years plus ET (preferentially with an AI) should be considered in high-risk premenopausal patients who recover ovarian function in the first 12–18 months after CT	I, A
In patients treated with OFS, regular monitoring of estrogen levels should be performed during the first year, especially in younger patients in whom OFS is achieved with LHRH analogues	I, A
In premenopausal patients becoming postmenopausal during the first 2–5 years of tamoxifen, a switch to an AI should be considered after evaluating the risk of late recurrence	II, A
If there is intermediate or high clinical risk of relapse, the total duration of adjuvant ET should be 7.5–8 years	I, A
Recommendations for endocrine therapy in postmenopausal patients	
For postmenopausal women, both non-steroidal and steroidal AIs are superior to tamoxifen	I, A
Adjuvant ET for postmenopausal patients may consist of any of the following alternatives, after considering risk factors and individual preferences:	I, A
– Upfront AI	
– AI after 2–3 years of tamoxifen	
– AI after 5 years of tamoxifen (letrozole and anastrozole) as extended adjuvant therapy, especially in intermediate- to high-risk (node-positive) patients	
Extended adjuvant therapy (optimal duration 7.5–8 years) should be discussed with all patients, except those with a very low risk of relapse	I, A
Extended adjuvant therapy with AI for > 8 years offers minimal benefit	I, C
In high-risk postmenopausal patients or those who decline or do not tolerate AI, 10 years of tamoxifen should be considered	I, A
General recommendations for adjuvant treatment	
Adjuvant bisphosphonates are recommended in postmenopausal women, and women undergoing ovarian suppression who are at high risk of recurrence and/or treatment-related bone loss	I, A
MAF test is an option to identify patients who would not add adjuvant bisphosphonates in their adjuvant hormone treatment	III, B
Adjuvant abemaciclib for 2 years in combination with adjuvant ET should be considered in high-risk patients (defined as tumors with ≥ 4 positive nodes or 1–3 nodes and either tumor size > 5 cm or histologic grade 3, independent of Ki67 levels)	I, A
Adjuvant ribociclib for 3 years in combination with AI-based ET may be considered in high- and intermediate-risk	I, B

Table 3 (continued)

Recommendation	Category, grade
Adjuvant olaparib for 1 year in combination with adjuvant ET should be considered in patients with germline pathogenic <i>BRCA</i> mutations, treated with adjuvant or NAC, and in patients with high-risk tumors (defined as tumors with ≥ 4 positive nodes in those who are ER-positive)	I, A
Triple negative or ER-positive patients treated with NAC who do not achieve a pCR (CPS + EG score of > 3 in the ER-positive group) are also candidates for this treatment	I, A
Recommendations for adjuvant CT	
Adjuvant CT for HR-positive, HER2-negative breast cancer is recommended for high-risk tumors defined by either clinical or genomic characteristics: T2–4 and/or axillary node involvement N2–3, extensive LVI, high Ki67, low ER expression, younger age or premenopausal status, and intermediate- to high-risk genomic score	I, A
Adjuvant CT has some benefit and may be considered in premenopausal patients with node-negative tumors and a recurrence score between 16 and 25	II, B
Sequential anthracycline/taxane-based regimen is the standard for most patients	I, A
CT should be administered for 12–24 weeks (4–8 cycles)	I, A
AC or EC are the standard anthracycline-based regimens, which should not include 5-FU	I, A
The use of dose-dense schedules (with granulocyte colony-stimulating factor support) should be considered in patients with high-risk tumors	I, A
In selected lower-risk patients, four cycles of taxane- or anthracycline-based CT or CMF may be used	II, B
Non-anthracycline regimens may be used in patients at risk for cardiac complications	I, A
One-year adjuvant olaparib should be offered to HR-positive, HER2-negative patients carrying a germline pathogenic variant in <i>BRCA1/2</i> with high-risk features (stage pN2 in patients treated with adjuvant CT, or high-risk defined as clinical and pathological stage and ER status and histologic grade score > 3 without pCR in patients treated with NST)	I, A
In patients aged approximately 50 years and/or of uncertain menopausal status, anti-Müllerian hormone levels > 10 pg/mL might be useful for decision making regarding use of CT	II, C
Recommendations for male patients with breast cancer	
In male patients with HR-positive, HER2-negative breast cancer, tamoxifen is the standard treatment	III, A
In male patients with HR-positive, HER2-negative breast cancer and a strong contraindication for tamoxifen, a combination of an AI plus a LHRH agonist may be considered	III, B
CT indications and regimens should follow the same recommendations as those for breast cancer in female patients	III, A
Recommendations for neoadjuvant therapy	
In patients with HR-positive, HER2-negative breast cancer, neoadjuvant treatment is recommended in locally advanced tumors and in those situations where a decrease in the extent of surgery is needed	I, A
CT drugs and drug regimens used in the preoperative setting should be selected according to rules identical to those in the postoperative setting	I, A
A sequential regimen of anthracyclines and taxanes is recommended in those patients in whom NAC is indicated for HR-positive and HER2-negative breast cancer	I, B
NET alone may be offered to those postmenopausal patients with strongly HR-positive tumors (ER $> 60\%$, or ER 40–60% and PgR $> 10\%$)	I, A
NET in postmenopausal patients should include an AI for at least 6–8 months or until maximum response	II, B
NET with AI plus ovarian suppression might be considered in highly selected premenopausal patients with luminal A-like tumors with no indication for CT and who are not candidates for optimal surgery	II, C
Gene expression-based assays in core needle biopsy may predict response to neoadjuvant therapy, although their use is currently considered experimental	II, C
Neoadjuvant and adjuvant systemic treatment of HER2-positive breast cancer	
Patients with HER2-positive tumors > 2 cm in size and/or node-positive disease should be treated with NST including dual HER2 blockade with trastuzumab and pertuzumab and CT with sequential taxanes/anthracyclines or taxane/carboplatin combinations	I, A
Selection of neoadjuvant regimens without anthracyclines may be used if seeking to avoid cardiotoxicity	II, B
HER2DX may be used to provide estimates of the likelihood of achieving pCR and of the risk of recurrence	II, B
Addition of standard 12-month adjuvant trastuzumab to CT is recommended for HER2-positive breast cancer both in node-positive and node-negative tumors with a tumor size > 1 cm	I, A
Addition of adjuvant trastuzumab to CT may be considered in cases of node-negative HER2-positive breast cancer with tumor size of 0.5–1.0 cm	II, B

Table 3 (continued)

Recommendation	Category, grade
For adjuvant CT of HER2-positive breast cancer, four cycles of AC or EC followed by 3 months of paclitaxel (P) or docetaxel (D) or both in combination with trastuzumab (AC/EC → P/D + H) or docetaxel, carboplatin and trastuzumab (TCH) are the preferred regimens	I, A
In node-negative, stage I, HER2-positive tumors, single-agent weekly paclitaxel and trastuzumab for 12 weeks followed by single-agent trastuzumab (to complete 1 year) should be considered	II, B
Adjuvant dual HER2 blockade with trastuzumab and pertuzumab for 18 cycles may be considered in patients with node-positive, HER2-positive breast cancer. In clinically node-positive patients who have received neoadjuvant treatment, up to 18 cycles of pertuzumab may be continued after surgery	I, A
Extended adjuvant treatment with neratinib after 1 year of trastuzumab may be considered in patients with node-positive and HR-positive, HER2-positive breast cancer	I, B
In patients with pCR after standard NST, adjuvant therapy with trastuzumab should be administered until one full year of total anti-HER2 therapy has been completed	I, A
In patients with pCR after standard NST and node-positive disease at diagnosis, addition of pertuzumab to adjuvant therapy with trastuzumab may be considered	II, B
Adjuvant T-DM1 for 14 cycles, instead of trastuzumab, should be considered in patients with HER2-positive breast cancer and residual disease after standard NST	I, A
In patients with HER2-positive, HR-positive breast cancer, adjuvant ET should be administered following the same principles as in HER2-negative HR-positive disease	I, A
Adjuvant and neoadjuvant systemic treatment for triple-negative breast cancer	
When upfront surgery followed by adjuvant CT is the preferred option for TNBC, the regimen should include an anthracycline and a taxane, although a taxane-cyclophosphamide or taxane/carboplatin combination might be an alternative in patients at high risk for cardiac toxicity	I, B
Adjuvant CT may be considered for 0.6–1 cm tumors after discussing potential risks and benefits with the patient	III, B
In early-stage TNBC, neoadjuvant systemic therapy is the preferred approach for cT1c–4 N0 or node-positive disease	I, A
NAC for TNBC should include anthracyclines and taxanes, preferably with dose-dense sequential regimens	I, A
Carboplatin improves the pCR rate and event-free survival and may be considered as part of NAC for TNBC patients	I, A
Addition of neoadjuvant pembrolizumab to NAC should be considered in the neoadjuvant setting for cT2–4 N0–3 TNBC, irrespective of PD-L1 expression. Adjuvant pembrolizumab might be administered as adjuvant treatment	I, A
In patients with triple-negative cT1cN0 tumors treated with NST, the recommended regimen is CT without pembrolizumab	I, A
Adjuvant capecitabine for 6–8 cycles should be considered in high-risk TNBC with residual invasive disease at surgery following standard NAC	I, B
Adjuvant olaparib for 1 year should be considered in individuals with germline <i>BRCA1/2</i> mutations and high-risk TNBC with residual invasive disease at surgery following standard NAC	I, A
Adjuvant combined or sequential use of pembrolizumab (with either capecitabine or olaparib) may be considered in patients with residual disease	III, C
Follow-up of early breast cancer	
Healthy lifestyles, especially an active lifestyle, are recommended to prevent tumor recurrence and to improve quality of life	II, B
Regular follow-up visits are recommended every 3–6 months during the first 2 years, every 6 months from years 3–5, and annually thereafter	III, A
Annual ipsilateral (after BCS) and/or a contralateral mammography is recommended for follow-up of early breast cancer	II, A
MRI of the breast may be considered for follow-up of young patients with dense breast tissue or with genetic or familial predisposition	II, B
Ultrasound or contrast-enhanced mammography may be considered as an additional study under the indication of a radiologist in doubtful cases or when there is a contraindication to MRI	III, B
There is no demonstrated survival benefit of including tumor markers or imaging tests (other than breast imaging) in the follow-up of asymptomatic patients	I, D
Prompt diagnostic evaluation should be performed in patients with symptoms or abnormal findings on physical examination during follow-up	III, A

5-FU 5-fluorouracil, AC doxorubicin and cyclophosphamide, AI aromatase inhibitor, ALND axillary lymph node dissection, ASCO American Society of Clinical Oncology, BCS breast conserving surgery, CAP College of American Pathologists, CMF cyclophosphamide, methotrexate, and fluorouracil, CPS + ER clinical and pathological stage and estrogen receptor status and histologic grade, CT chemotherapy, DCIS ductal carcinoma in situ, EC epirubicin and cyclophosphamide, ER estrogen receptor, ET endocrine therapy, DCIS ductal carcinoma in situ, HER2 human epidermal growth factor receptor 2, HR hormone receptor, LHRH luteinizing hormone–releasing hormone, LVI lymphovascular invasion, MRI magnetic resonance imaging, NAC neoadjuvant chemotherapy, NET neoadjuvant endocrine therapy, NST neoadjuvant systemic therapy, OFS ovarian function suppression, PD-L1 programmed death-ligand 1, pCR pathologic complete response, PgR progesterone receptor, SLN sentinel lymph node, T-DM1 trastuzumab emtansine, TNBC triple-negative breast cancer

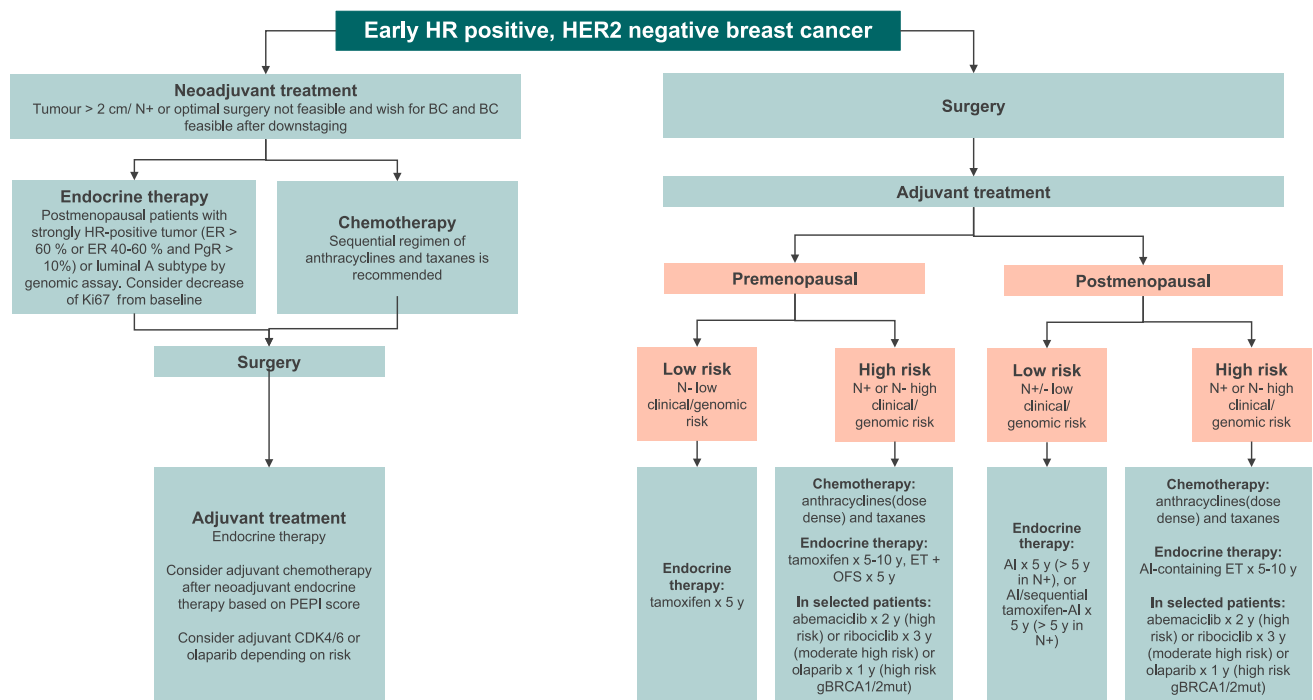


Fig. 1 HR-positive/HER2-negative early-stage breast cancer algorithm. *AI* aromatase inhibitors, *BC* breast conservation, *CDK4/6* cyclin-dependent kinases 4 and 6, *ER* estrogen receptor, *gBRCA1/2mut* germline *BRCA1/2* mutation, *HER2* human epidermal growth factor

receptor 2, *HR* hormone receptor, *N* axillary node, *OFS* ovarian function suppression, *PEPI* Preoperative Endocrine Prognostic Index, *PgR* progesterone receptor, *yr(s)* year(s)

Oncotype DX[®] is recommended in premenopausal patients with node-negative tumors (I, A). Based on results from the TAILORx trial [19], CT has some benefit for distant recurrence if the recurrence score is 16–25 (II, B).

Oncotype DX[®], MammaPrint[®], and EndoPredict[®] can be useful to guide adjuvant treatment in postmenopausal patients or those > 50 years old with node-negative tumors or who have 1–3 positive nodes (I, A; I, A; II, B) [17]. In addition, Prosigna[®] may be used as a standard option in postmenopausal patients with node-negative tumors (II, A) [52].

Dynamic changes in Ki67 after 2 weeks of perioperative ET in postmenopausal women can be considered a surrogate prognostic factor based on the POETIC trial (II, B) [53]. According to results from the WGS-ADAPT and ADAPTCycle trials, dynamic changes in Ki67 after 4 weeks of preoperative OFS and an aromatase inhibitor (AI) in premenopausal patients with a recurrence score of 0–25 might provide further prognostic stratification to determine the expected benefit of adjuvant CT (II, C) [54, 55].

Systemic treatment for early-stage luminal-type breast cancer

Adjuvant endocrine therapy

There is robust evidence that ET improves survival of early-stage luminal breast cancer. Adjuvant ET should be offered to all HR-positive patients regardless of age, menopausal status, CT exposure, hormone expression level (ER or PgR; if any or both are positive defined as ER > 1% and/or PgR > 10%), and/or HER2 status (I, A) [56]. There are several ET options. The individual choice should be adjusted to menopause status, comorbidity, expected toxicities and risk of recurrence. Adjuvant systemic therapy is best started without undue delays, as data reveal an important decrease in efficacy when it is administered > 12 weeks after surgery (I, A) [57] (Fig. 1).

Premenopausal patients

Tamoxifen for 5 years is the most widely established adjuvant ET for low-risk (stage I) premenopausal patients (I, A) [58]. It should be considered for up to 10 years in patients with higher-risk tumors in the presence of ovarian function (at the expense of greater toxicity) (I, B) [59, 60]. In

high-risk premenopausal patients who recover menses or ovarian function after CT (in the first 12–18 months), the addition of ovarian function suppression (OFS) for 2 to 5 years plus ET should be offered (I, A), the most effective combination being with AIs [61, 62]. In patients treated with AIs plus chemical OFS, clinicians should monitor estrogen levels biochemically at regular intervals (I, A), mainly in younger patients during the first year of treatment. Luteinizing hormone–releasing hormone (LHRH) analogues should be administered in a monthly or 3-monthly schedule for these patients (depending on patient preference and optimization of ovarian suppression), for a total duration of 2.5–5 years (I, A).

In patients who become postmenopausal during the first 2–5 years of tamoxifen treatment, a switch to AIs should be considered, depending on risk of late recurrence (II, A). The total duration of adjuvant ET should be 7.5–8 years if there is intermediate or high clinical risk of relapse (I, A).

Postmenopausal patients

For postmenopausal women, AIs (both non-steroidal and steroidal) are superior to tamoxifen (I, A), although their use should be individualized based on patient tolerance and drug toxicity profiles. AIs can be used upfront (non-steroidal AI and exemestane), after 2–3 years of tamoxifen (non-steroidal AI and exemestane), or as extended adjuvant therapy after 5 years of tamoxifen (letrozole and anastrozole) (I, A), especially in intermediate- to high-risk patients [63–68].

Extended adjuvant therapy should be discussed with all patients, except for those with a very low risk of relapse (I, A). In patients undergoing extended therapy, the optimal duration of ET is 7.5–8 years; and there is only a minimal benefit from the use of AIs for > 8 years (I, C) [69]. The predictive benefit of the Breast Cancer Index for extended ET has been demonstrated in various cohorts that include patients with 0–3 involved lymph nodes [70–72].

The option of 10 years of tamoxifen could be considered in high-risk postmenopausal patients, or those who decline or have a contraindication to AIs (I, A).

Other therapies in the adjuvant setting

Bisphosphonates

Bisphosphonates are recommended in women who are postmenopausal, or undergoing ovarian suppression who are at high risk of recurrence and/or treatment-related bone loss (I, A) [73, 74]. Testing for tumor expression of the transcription factor, MAF (a biomarker for bone metastasis) may be useful to identify patients who will benefit from adjuvant

bisphosphonates. Analyses of MAF expression in patients treated with zoledronate or clodronate found better outcomes (iDFS, DFS, and overall survival [OS]) in patients with MAF-negative tumors [75–77]. Indeed, patients with MAF-positive tumors may experience more extraskelatal recurrences [76]. The MAF-Test™ may be an option to identify MAF-negative patients with a higher benefit of adjuvant bisphosphonates and those in whom these treatments should be avoided (III, B).

Cell cycle inhibitors

Adjuvant abemaciclib for 2 years in combination with ET is indicated in high-risk patients, defined as those with tumors with > 4 positive nodes, or 1–3 nodes and tumor size > 5 cm or histologic grade 3, independent of Ki67 levels (I, A) based on the results of the monarchE trial (5-year absolute invasive disease-free survival [iDFS] benefit 7.6%) [78].

Based on updated NATALEE trial results (44-month absolute iDFS benefit 4.9%), adjuvant ribociclib for 3 years in combination with AI-based ET may be considered in high- and intermediate-risk patients, defined according to the NATALEE trial inclusion criteria of stages IIB–III, or stage IIA pN0 with high-risk features (grade 3 or grade 2 plus either high genomic risk or Ki67 > 20%) (I, B) [79].

PARP inhibitors

In the OlympiA trial, 1-year adjuvant olaparib demonstrated improved 4-year OS (89.9% vs 86.4% with placebo) and iDFS (82.7% vs 75.4% with placebo) in patients with HER2-negative breast cancer with *BRCA1* or *BRCA2* germline pathogenic mutations, and with high-risk clinic-pathological features (at least four pathologically-confirmed positive lymph nodes in the ER-positive population) [80]. Triple negative or ER-positive patients treated with neoadjuvant chemotherapy (NAC) who do not achieve a pCR (clinical and pathological stage and ER status and histologic grade [CPS + EG] score of ≥ 3 in the ER-positive group) are also candidates for this treatment (I, A) [81]. Other patients with high-risk gBRCA-mutated tumors should receive adjuvant olaparib in an individualized manner.

Adjuvant chemotherapy in hormone receptor-positive disease

The use of CT as adjuvant treatment for ER-positive, HER2-negative disease is recommended for high-risk tumors defined by either clinical or genomic profiling characteristics (I, A), considered to be: T2 to T4 tumors and/or axillary N2–3 involvement; extensive lympho-vascular invasion; high Ki67; low ER expression; younger age or premenopausal

status, and intermediate- to high-risk genomic score. In premenopausal patients under 55 years of age, recent unpublished post-hoc data from the RxPonder trial suggest the potential utility of anti-Müllerian hormone (AMH) levels to predict the benefit of adjuvant CT. In patients aged 50 to 55 years and/or of uncertain menopausal status, AMH levels > 10 pg/mL might be useful for decision making regarding use of CT (II, C) [82].

CT should be administered for 12–24 weeks (4–8 cycles) (I, A). A sequential anthracycline/taxane-based regimen is the standard for most patients (I, A). Anthracycline-based regimens should not include 5-fluorouracil (5-FU); epirubicin and cyclophosphamide [EC] or doxorubicin and cyclophosphamide (AC) are standard (I, A) [83, 84]. Since many patients treated with adjuvant CT are included in the high-risk category, the use of dose-dense schedules (with granulocyte colony-stimulating factor support) should be considered in most patients (I, A) [85, 86]. In selected lower-risk patients, four cycles of taxane-or anthracycline-based CT or cyclophosphamide, methotrexate, and fluorouracil (CMF) may be used (II, B) [87, 88]. Non-anthracycline regimens may be used in patients at risk for cardiac complications (I, A) [88]. One-year adjuvant olaparib should be offered to HR-positive, HER2-negative patients carrying a germline pathogenic variant in *BRCA1/2* with high-risk features (stage pN2 in patients treated with adjuvant CT, or high-risk defined as clinical and pathological stage and ER status and histologic grade score > 3 without pCR in patients treated with NST), based on the results of the OlympiA trial (I, A) [80].

In male patients, tamoxifen is the standard adjuvant systemic therapy (III, A); AIs should not be used alone in this setting. If a strong contraindication exists for the use of tamoxifen, a combination of an AI plus a LHRH analogue may be considered (III, B). CT indications and regimens should follow the same recommendations as those for breast cancer in female patients (discuss with patients higher toxicity and compliance) (III, A) [89–91].

Neoadjuvant treatment in hormone receptor-positive disease

Neoadjuvant treatment is recommended in locally advanced tumors and in those situations where a decrease in the extent of surgery is needed (I, A). The timing of treatment (pre- versus postoperative) has no effect on long-term outcomes, except a possible small increase in locoregional recurrences, but without impact on survival (II, A) [92].

Neoadjuvant endocrine therapy (NET) alone may be offered to those postmenopausal patients with strongly

HR-positive tumors (ER > 60%, or RE 40–60% and PgR > 10%) (I, A). AIs are more effective than tamoxifen in decreasing Ki67 levels and tumor size, and facilitating less extensive surgery (I, A) [93, 94]. The preferred ET option for postmenopausal patients is an AI for at least 6–8 months or until maximum response (II, B). NET is not routinely recommended in premenopausal patients, outside of clinical trials. However, in highly selected patients with luminal A-like tumors and no indication for CT, who are not candidates for optimal surgery, OFS plus an AI can be considered (II, C) [95]. In clinical trials comparing NET and CT, similar response rates were observed but with a significantly lower toxicity for NET (II, B) [96].

The efficacy evaluation of NET has been performed according to surrogate parameters such as the decrease of the Ki67 levels during the first cycle of NET, or the Preoperative Endocrine Prognostic Index (PEPI) score after surgery (II, B) [97]. Different gene expression-based assays have been evaluated in core needle biopsy before neoadjuvant therapy, as good predictors of treatment response, although this approach is currently considered experimental (II, C) [98].

CT drugs and drug regimens used in the preoperative setting should be selected according to rules identical to those in the postoperative setting (I, A). A sequential regimen of anthracyclines and taxanes is recommended for the vast majority of patients (I, B).

Systemic treatment for HER2-positive early-stage breast cancer

Neoadjuvant treatment

Response to neoadjuvant treatment in HER2-positive breast cancer provides useful information on pathological response, which is considered a reliable surrogate marker of disease-free survival (DFS) and potentially OS [99]. Residual disease after neoadjuvant treatment also allows tailoring of adjuvant treatment after surgery.

Patients with $\geq$ cT2 tumors or cN-positive disease should be treated with standard CT (taxane-AC/EC or taxane with or without carboplatin) plus dual HER2 blockade with pertuzumab plus trastuzumab [100]. The efficacy of this dual HER2 blockade has been endorsed by the latest analysis of the APHINITY study, confirming an OS benefit in the early setting for node-positive tumors at diagnosis [101] (I, A) (Fig. 2).

Established NAC regimens are either an anthracycline-taxane sequence plus pertuzumab plus trastuzumab or docetaxel-carboplatin plus dual HER2 blockade, for a minimum of 9 weeks of taxane plus anti-HER2 therapy. Recently, the TRAIN-2 study suggested that an

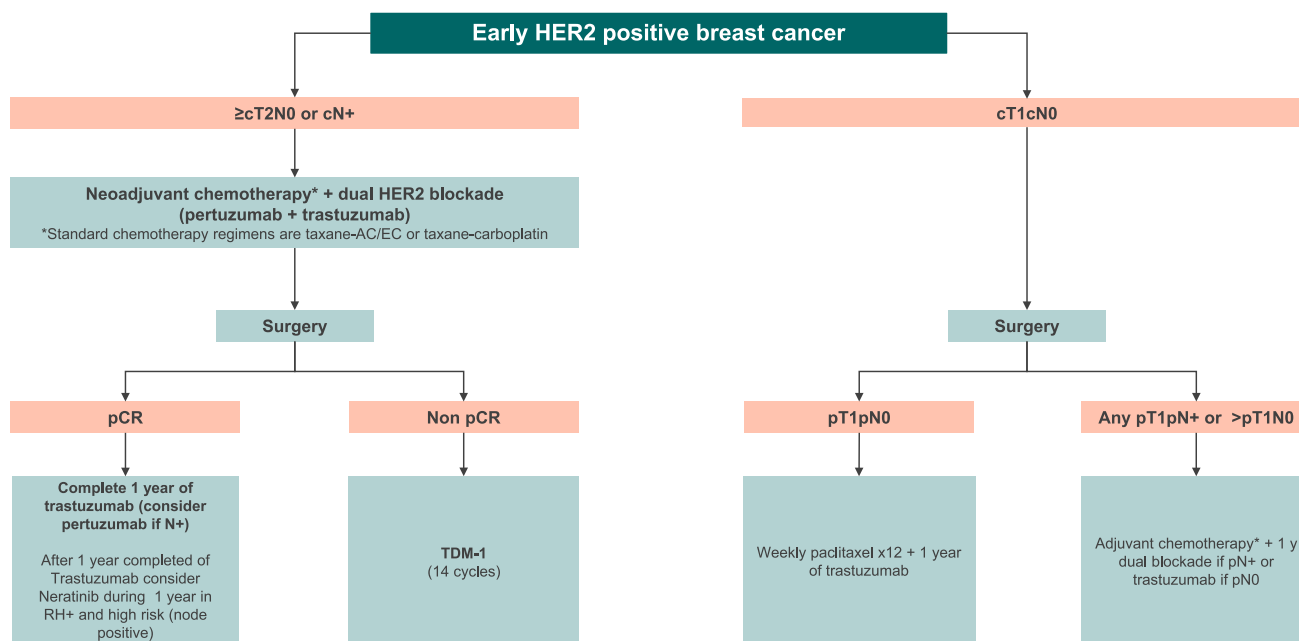


Fig. 2 HER2-positive early-stage breast cancer algorithm. *cN* clinically positive axillary node, *cT* clinical tumor stage, *HER2* human epidermal growth factor receptor 2 positive, *N* axillary node, *pCR* pathologic complete response, *pN* primary node, *pT* primary tumor, *T* tumor, *TDM-1* trastuzumab emtansine, *yr* year. *Standard chemo-

therapy regimens are taxane-doxorubicin and cyclophosphamide/epirubicin and cyclophosphamide, or taxane-carboplatin. ^bOne year after completing trastuzumab, consider neratinib for 1 year in hormone receptor-positive and high risk (N-positive) patients. This treatment is still awaiting financial approval from the health authorities in Spain

anthracycline combination does not increase efficacy in terms of pCR or patient outcomes versus a sequential taxane-platinum containing regimen with dual antibody blockade, and with similar long-term outcomes [102]. The evidence for anthracycline-free CT in HER2-positive early breast cancer was reinforced in the neoadjuvant setting by the results of the TRY-PHAENA trial [103], and in the adjuvant setting by the BCIRG-006 trial [104]. The incidence of significant declines in left ventricular ejection fraction is lower without anthracycline-containing regimens so this could be the chosen CT backbone if seeking to avoid cardiotoxicity (II, B).

HER2DX could help to identify suitable candidates for escalation and de-escalation treatment strategies in some clinical situations. It could be used in patients with HER2-positive tumors who plan to undergo NST to aid decision-making regarding CT agents to use in combination with dual HER2 blockade with trastuzumab and pertuzumab. Additional prospective validation is ongoing (II, B) [105].

Adjuvant treatment

The administration of trastuzumab plus adjuvant CT reduces the risk of relapse and mortality, regardless of tumor size, age, and nodal and HR status [104, 106, 107]. The optimal duration of trastuzumab treatment has been

established as 12 months (I, A) [108, 109]. It may be safely combined with either RT or ET. Adjuvant trastuzumab is recommended in all tumors > 1 cm regardless of nodal status (I, A), and might be considered in node-negative tumors of 0.5–1 cm, especially in patients with ER-negative disease, although no level I evidence exists for such use (II, B). Thus, four cycles of AC or EC followed by 3 months of paclitaxel or docetaxel, both in combination with trastuzumab (AC/EC → P/D + H), or docetaxel, carboplatin, and trastuzumab (TCH) are preferred regimens (I, A).

In patients with stage I disease, treatment with paclitaxel for 12 weeks in combination with trastuzumab followed by 1 year of single-agent trastuzumab should be considered, based on the results of the phase II APT trial (II, B) [22].

In the APHINITY trial [101, 110], the addition of pertuzumab demonstrated a modest but significant iDFS and OS benefit in node-positive patients who had not received neoadjuvant therapy, regardless of HR status. Based on this trial, the European Medicines Agency (EMA) approved the use of 18 cycles of dual trastuzumab plus pertuzumab treatment in the high-risk node-positive population, regardless of whether it was initiated in the adjuvant or neoadjuvant setting (I, A). Despite this evidence, Spanish health authorities have declined to fund the adjuvant indication for pertuzumab.

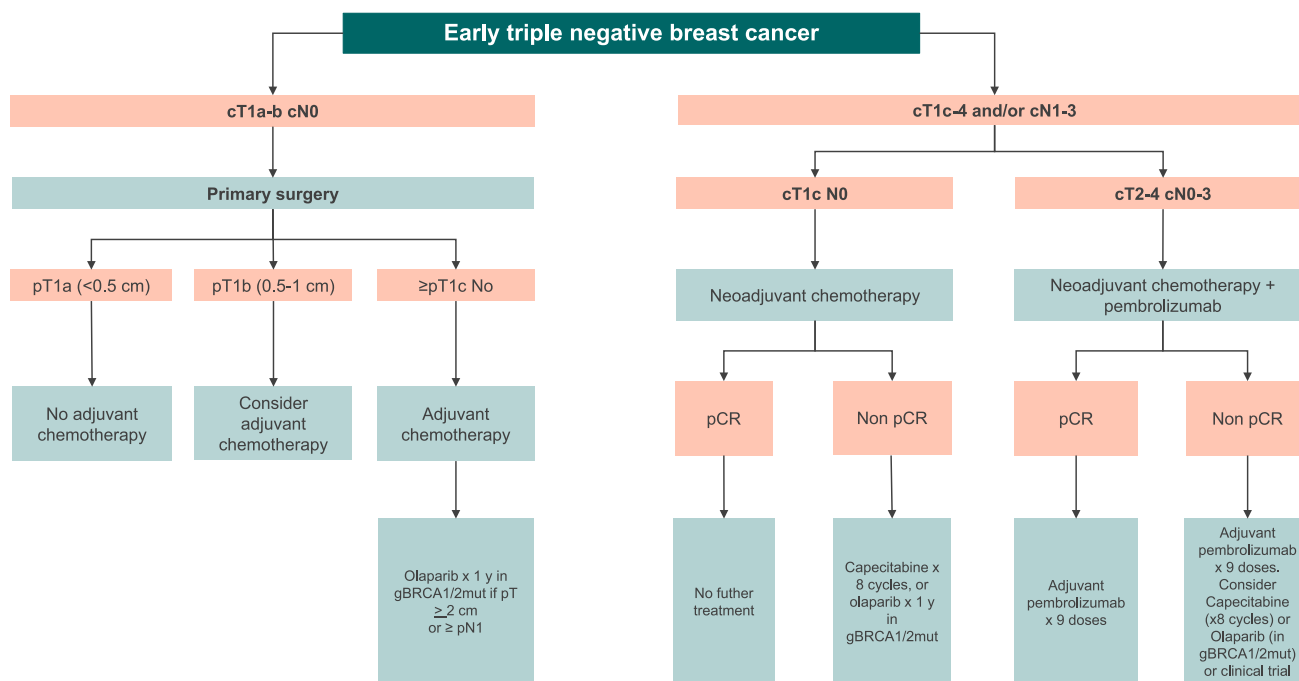


Fig. 3 Triple-negative early-stage breast cancer algorithm. *cN* clinically positive axillary node, *cT* clinical tumor stage, *gBRCA1/2mut* germline BRCA1/2 mutation, *N* axillary node, *pCR* pathologic complete response, *pN* primary node, *pT* primary tumor, *T* tumor, *yr* year

The addition of 1 year of adjuvant neratinib improved iDFS in patients with HER2-positive breast cancer after 1 year of trastuzumab in the phase III EXTENET trial [111]. The benefit was greater in patients with HR-positive and node-positive disease, at the expense of increased toxicity (diarrhea) (I, B). Neratinib has been approved by the EMA, which restricted its use to HR-positive disease. The authorities in Spain also restrict its use to patients who have not completed 1 year of trastuzumab for any reason.

In patients who received neoadjuvant treatment (minimum 6 cycles with at least 9 weeks of taxane plus trastuzumab regimen) and who did not achieve pCR, 14 cycles of adjuvant trastuzumab emtansine (T-DM1) substantially improved outcomes compared with adjuvant trastuzumab in the KATHERINE trial, with a substantial difference in 7-year iDFS (80.8% vs 67.1%) and OS (89.1% vs 84.4%). This benefit was seen independently of adjuvant ET, RT or HER2 status in the residual disease [112] (I, A).

For those with pCR, adjuvant anti-HER2 therapy with trastuzumab should be administered until a full year of total anti-HER2 therapy has been completed (I, A). Patients with node-positive disease at diagnosis may receive adjuvant pertuzumab added to trastuzumab, as suggested by the results of the APHINITY trial [101, 113] (II, B),

In patients with HER2-positive, HR-positive breast cancer, adjuvant ET should be administered following the same principles as for patients with HER2-negative disease.

No evidence exists to support the use of adjuvant CDK4/6 inhibitors or PARP inhibitors in HER2-positive early breast cancer.

Systemic treatment for triple-negative breast cancer

Adjuvant treatment

TNBC is a heterogeneous disease that accounts for approximately 15–20% of all breast cancers [114]. It tends to comprise high-grade tumors with a high proliferation index and a particular trend to metastasize early to organs such as liver, lung, and central nervous system [115].

While historically, surgery and adjuvant CT have been considered the cornerstone of early TNBC treatment, NST has emerged as the preferred option, not just in locally advanced tumors but also in smaller tumors. Since systemic therapy should be considered in all stage I tumors (except in those ≤ 5 mm, with an excellent prognosis without CT) [116], administration of NST could yield locoregional benefits and offer response information (Fig. 3). Nevertheless, when upfront surgery and adjuvant CT is the preferred option, the regimen should include an anthracycline and a taxane (I, B), although a taxane/cyclophosphamide or taxane/platinum combination can represent a good alternative in patients with potential cardiac toxicity (I, B) [117,

[118]. CT should be discussed with patients with pT1b N0 (6–10 mm) tumors, weighing potential risks and benefits in this good prognosis group [116] (III, B). High levels of tumor infiltrating lymphocytes are associated with better short and long-term outcomes, and can be useful for selection of adjuvant CT regimens [119].

Neoadjuvant treatment

In early-stage TNBC, NST is the preferred approach for cT1c–4 N0 or node-positive disease (I, A). This recommendation follows European guidelines [120].

NST with CT or NAC is the preferred approach in locally advanced (stage II–III) TNBC, leading classically to pCR rates of 30–40% [121]. Patients who achieve a pCR have an excellent prognosis. Residual disease after NAC is a recognized biomarker associated with an increased recurrence risk that can be very useful when selecting patients for post-neoadjuvant escalating therapies.

The combination of anthracyclines and taxanes is the treatment of choice (I, A), preferably with dose-dense sequential regimens. A meta-analysis of nine randomized, controlled trials investigating platinum-based versus platinum-free NAC in TNBC reported an increase in pCR from 37.0% to 52.1% with platinum-based regimens [121]. A more recent meta-analysis showed improved long-term DFS and OS with carboplatin [117], indicating that this agent should be added to CT based on taxane or sequential taxane and anthracycline regimens (I, A).

The recent incorporation of immunotherapy to NAC regimens for TNBC has changed the “CT-only” neoadjuvant approach in these patients. In patients with triple-negative cT1cN0 tumors treated with NST, the recommended regimen is CT without pembrolizumab (I, A). For cT2–4 N0–3 tumors, based on the updated results of the phase III KEY-NOTE-522 trial [122], which showed a benefit in 5-year OS (86.6% vs 81.7%) and 5-year event-free survival (EFS) in both the pCR (92.2% vs 88.2%) and non-pCR (62.6% vs 52.3%) groups [123], pembrolizumab should be added to CT in the neoadjuvant setting and continued in the adjuvant setting, irrespective of programmed death-ligand 1 (PD-L1) expression and pCR status (I, A).

As stated above, patients with residual disease after NAC have a significant risk of recurrence, particularly in the first 2–3 years following diagnosis. In the post-neoadjuvant setting, the administration of 6–8 cycles of capecitabine represents a good therapeutic option, based on the results of the CREATE-X trial [124] and a meta-analysis [125] (I, B). One-year adjuvant olaparib should be offered to patients with TNBC who carry a germline pathogenic variant in *BRCA1/2* and without pCR after NST, or after adjuvant CT in patients with tumors > 2 cm (> pT2) or lymph node (> pN1) involvement in primary surgery cases (I, A). This

is based on the results of the OlympiA trial, which showed a significant increase in 4-year iDFS (82.7% vs 75.4%) and OS (89.8% vs 86.4%) in this population [80]. Although no supportive data are available, adjuvant combined or sequential use of pembrolizumab (with either capecitabine or olaparib) may be considered in patients with residual disease (III, C).

Follow-up, long-term implications, and survivorship

Breast cancer follow-up should focus on detecting disease relapse or second primary neoplasms. Although there is no universal sequence or protocol for the follow-up of these patients, taking into account both patient needs and follow-up costs, regular visits are recommended every 3–6 months in the first 2 years, every 6 months after 3–5 years, and annually thereafter (III, A). As part of monitoring, each visit should include a thorough anamnesis, record of symptoms, and physical examination. Annual ipsilateral (after BCS) and/or contralateral mammography (after mastectomy) is recommended (II, A). An MRI of the breast may be indicated for young patients, especially in cases of dense breast tissue and genetic or familial predisposition [126] (II, B). Ultrasound may be considered only as an additional study under the indication of a radiologist in doubtful cases or when there is a contraindication for MRI; contrast-enhanced mammography might also be indicated in these cases (III, B) [127]. Routine imaging of reconstructed breast is not indicated.

There are no data to indicate that either laboratory or imaging tests or any tumor markers, such as cancer antigen 15-3 (CA15-3) or carcinoembryonic antigen (CEA), result in a survival benefit (I, D). In symptomatic patients or in the case of abnormal findings on examination, appropriate and specific tests should be performed immediately (III, A) [127].

It is also important to evaluate and manage the toxicities of the treatment received, both physical and psychosocial, in the short and long term. Patients on tamoxifen treatment will require age-appropriate gynecological screening. Those on an AI or who experience ovarian failure secondary to treatment should undergo monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter [127]. Finally, healthy lifestyle habits, such as an active lifestyle (II, B), a healthy diet, limited alcohol consumption, and achieving and maintaining an ideal body weight (body mass index 20–25 kg/m²) can lead to optimal breast cancer outcomes and improved quality of life [127].

A summary of the SEOM recommendations/clinical practice guidelines for early-stage breast cancer is shown in Table 3.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12094-025-04139-x>.

Acknowledgements The authors thank César Rodríguez Sánchez and Juan de la Haba Rodríguez for their review and validation of the levels of evidence and grades of recommendation in this guideline. The authors also thank Kate Palmer and Ana Moreno of Springer Health+, who provided editorial assistance with updating the guideline.

Author contributions The Spanish Society of Medical Oncology (SEOM) was responsible for the article conception. All authors were equally responsible for this work; all authors performed the literature search and data analysis, drafted and/or critically revised the manuscript, and approved the final version.

Funding This work was funded by the Spanish Society of Medical Oncology (SEOM). Open Access funding was provided thanks to the CRUE-CSIC agreement with Springer Nature.

Data availability Data sharing is not applicable to this article as no datasets were generated or analyzed.

Declarations

Conflict of interest Francisco Ayala de la Peña has received fees for speaking and participating in advisory boards from AstraZeneca, Novartis, Lilly, Sanofi, Daiichi Sankyo, Celgene, Eisai, Pierre Fabre, Pfizer, Roche, MSD, and Seagen. Joaquín Gavilá Gregori has received fees for speaking and participating in advisory boards from Daiichi Sankyo, AstraZeneca, Novartis, Roche, Pfizer, and Lilly. Fernando Henao Carrasco has received fees for participating in advisory boards from AstraZeneca, Daiichi-Sankyo, Novartis, Pfizer, Lilly, and Roche. Agostina Stradella has received fees for speaking and participating in advisory boards from AstraZeneca, Daiichi-Sankyo, Novartis, MSD and Gilead. Eva Ciruelos has received fees for speaking and participating in advisory boards from Roche, Lilly, Pfizer, AstraZeneca, Daiichi Sankyo, Novartis, MSD, Gilead, and Reveal Genomics. Silvia Antolín Novoa, Lucía González Cortijo, María Teresa Martínez Martínez, Cristina Morales Estévez, and María Jesús Vidal Losada declare that they have no conflicts of interest.

Ethics approval and informed consent Not applicable. The manuscript does not contain clinical studies or patient data.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Sociedad Española de Oncología Médica (SEOM) RE de R del C (REDECAN). Breast cancer [Internet]; 2023 [cited 2025 June 10]. <https://seom.org/info-sobre-el-cancer/cancer-de-mama?start=2>. Accessed 10 June 2025
2. Bosch G, Posso M, Louro J, Roman M, Porta M, Castells X, et al. Impact of the COVID-19 pandemic on breast cancer screening indicators in a Spanish population-based program: a cohort study. *Elife*. 2022;11:e77434. <https://doi.org/10.7554/eLife.77434>.
3. Khan AR, Khan S, Zimmerman V, Baddour LM, Tleyjeh IM. Quality and strength of evidence of the Infectious Diseases Society of America clinical practice guidelines. *Clin Infect Dis*. 2010;51(10):1147–56. <https://doi.org/10.1086/656735>.
4. Giuliano AE, Connolly JL, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, et al. Breast cancer—major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67:290–303. <https://doi.org/10.3322/caac.21393>.
5. Perry N, Broeders M, de Wolf C, Tornberg S, Holland R, von Karsa L. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition—summary document. *Ann Oncol*. 2008;19:614–22. <https://doi.org/10.1093/annonc/mdm481>.
6. Sardanelli F, Boetes C, Borisch B, Decker T, Federico M, Gilbert FJ, et al. Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. *Eur J Cancer*. 2010;46:1296–316. <https://doi.org/10.1016/j.ejca.2010.02.015>.
7. Lopez-Fernandez T, Martín García A, Santaballa Beltrán A, Montero Luis A, García Sanz R, Mazon Ramos P, et al. Cardio-onco-hematology in clinical practice. Position paper and recommendations. *Revista Española de Cardiología (English Edition)*. 2017;70:474–86. <https://doi.org/10.1016/j.rec.2016.12.041>.
8. Louie RJ, Tonneson JE, Gowarty M, Goodney PP, Barth RJ Jr, Rosenkranz KM. Complete blood counts, liver function tests, and chest x-rays as routine screening in early-stage breast cancer: value added or just cost? *Breast Cancer Res Treat*. 2015;154(1):99–103. <https://doi.org/10.1007/s10549-015-3593-y>.
9. Groheux D, Vaz SC, de Geus-Oei LF, Dibble EH, Ulaner GA, Cook GJR, et al. [(18)F]-labeled fluorodeoxyglucose-positron emission tomography/computed tomography in staging and restaging patients with breast cancer. *J Clin Oncol*. 2025;43:1942–7. <https://doi.org/10.1200/JCO.24-01945>.
10. Tan PH, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S, et al. The 2019 World Health Organization classification of tumours of the breast. *Histopathology*. 2020;77(2):181–5. <https://doi.org/10.1111/his.14091>.
11. WHO Classification of Tumours Editorial Board. Breast tumours: WHO classification of tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2019.
12. Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. *J Clin Oncol*. 2020;38:1346–66. <https://doi.org/10.1200/JCO.19.02309>.
13. Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. *Arch Pathol Lab Med*. 2018;142:1364–82. <https://doi.org/10.5858/arpa.2018-0902-SA>.
14. Nielsen TO, Leung SCY, Rimm DL, Dodson A, Acs B, Badve S, et al. Assessment of Ki67 in breast cancer: updated recommendations from the International Ki67 in Breast Cancer Working

- Group. *J Natl Cancer Inst.* 2021;113:808–19. <https://doi.org/10.1093/jnci/djaa201>.
15. Denkert C, von Minckwitz G, Darb-Esfahani S, Lederer B, Heppner BI, Weber KE, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. *Lancet Oncol.* 2018;19(1):40–50. [https://doi.org/10.1016/S1470-2045\(17\)30904-X](https://doi.org/10.1016/S1470-2045(17)30904-X).
 16. Wein L, Savas P, Luen SJ, Virassamy B, Salgado R, Loi S. Clinical validity and utility of tumor-infiltrating lymphocytes in routine clinical practice for breast cancer patients: current and future directions. *Front Oncol.* 2017;7:156. <https://doi.org/10.3389/fonc.2017.00156>.
 17. Kalinsky K, Barlow WE, Gralow JR, Meric-Bernstam F, Albain KS, Hayes DF, et al. 21-gene assay to inform chemotherapy benefit in node-positive breast cancer. *N Engl J Med.* 2021;385:2336–47. <https://doi.org/10.1056/NEJMoa2108873>.
 18. Piccart M, van 't Veer LJ, Poncet C, Lopes Cardozo JMN, Delaloge S, Pierga JY, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. *Lancet Oncol.* 2021;22:476–88. [https://doi.org/10.1016/S1470-2045\(21\)00007-3](https://doi.org/10.1016/S1470-2045(21)00007-3).
 19. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med.* 2018;379(2):111–21. <https://doi.org/10.1056/NEJMoa1804710>.
 20. Bueno-Muino C, Echavarria I, Lopez-Tarruella S, Roche-Molina M, Del Monte-Millan M, Massarrah T, et al. Assessment of a genomic assay in patients with ERBB2-positive breast cancer following neoadjuvant trastuzumab-based chemotherapy with or without pertuzumab. *JAMA Oncol.* 2023;9:841–6. <https://doi.org/10.1001/jamaoncol.2023.0187>.
 21. Prat A, Guarneri V, Pascual T, Braso-Maristany F, Sanfeliu E, Pare L, et al. Development and validation of the new HER2DX assay for predicting pathological response and survival outcome in early-stage HER2-positive breast cancer. *EBioMedicine.* 2022;75:103801. <https://doi.org/10.1016/j.ebiom.2021.103801>.
 22. Tolaney SM, Tarantino P, Graham N, Tayob N, Pare L, Villacampa G, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial. *Lancet Oncol.* 2023;24(3):273–85. [https://doi.org/10.1016/S1470-2045\(23\)00051-7](https://doi.org/10.1016/S1470-2045(23)00051-7).
 23. Waks AG, Ogayo ER, Pare L, Marin-Aguilera M, Braso-Maristany F, Galvan P, et al. Assessment of the HER2DX assay in patients with ERBB2-positive breast cancer treated with neoadjuvant paclitaxel, trastuzumab, and pertuzumab. *JAMA Oncol.* 2023;9:835–40. <https://doi.org/10.1001/jamaoncol.2023.0181>.
 24. Kimball CC, Nichols CI, Vose JG, Peled AW. Trends in lumpectomy and oncoplastic breast-conserving surgery in the US, 2011–2016. *Ann Surg Oncol.* 2018;25:3867–73. <https://doi.org/10.1245/s10434-018-6760-7>.
 25. Lautner M, Lin H, Shen Y, Parker C, Kuerer H, Shaitelman S, et al. Disparities in the use of breast-conserving therapy among patients with early-stage breast cancer. *JAMA Surg.* 2015;150(8):778–86. <https://doi.org/10.1001/jamasurg.2015.1102>.
 26. Carter SA, Lyons GR, Kuerer HM, Bassett RL Jr, Oates S, Thompson A, et al. Operative and oncologic outcomes in 9861 patients with operable breast cancer: single-institution analysis of breast conservation with oncoplastic reconstruction. *Ann Surg Oncol.* 2016;23:3190–8. <https://doi.org/10.1245/s10434-016-5407-9>.
 27. Jonczyk MM, Jean J, Graham R, Chatterjee A. Surgical trends in breast cancer: a rise in novel operative treatment options over a 12 year analysis. *Breast Cancer Res Treat.* 2019;173(2):267–74. <https://doi.org/10.1007/s10549-018-5018-1>.
 28. Burstein HJ, Curigliano G, Loibl S, Dubsky P, Gnant M, Poortmans P, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. *Ann Oncol.* 2019;30:1541–57. <https://doi.org/10.1093/annonc/mdz235>.
 29. Tung NM, Boughey JC, Pierce LJ, Robson ME, Bedrosian I, Dietz JR, et al. Management of hereditary breast cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline. *J Clin Oncol.* 2020;38:2080–106. <https://doi.org/10.1200/JCO.20.00299>.
 30. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. *JAMA.* 2017;318:918–26. <https://doi.org/10.1001/jama.2017.11470>.
 31. Gentilini OD, Botteri E, Sangalli C, Galimberti V, Porpiglia M, Agresti R, et al. Sentinel lymph node biopsy vs no axillary surgery in patients with small breast cancer and negative results on ultrasonography of axillary lymph nodes: the SOUND randomized clinical trial. *JAMA Oncol.* 2023;9:1557–64. <https://doi.org/10.1001/jamaoncol.2023.3759>.
 32. Reimer T, Stachs A, Veselinovic K, Kuhn T, Heil J, Polata S, et al. Axillary surgery in breast cancer—primary results of the INSEMA trial. *N Engl J Med.* 2025;392:1051–64. <https://doi.org/10.1056/NEJMoa2412063>.
 33. de Boniface J, Filtenborg Tvedskov T, Ryden L, Szulkin R, Reimer T, Kuhn T, et al. Omitting axillary dissection in breast cancer with sentinel-node metastases. *N Engl J Med.* 2024;390:1163–75. <https://doi.org/10.1056/NEJMoa2313487>.
 34. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol.* 2014;15:1303–10. [https://doi.org/10.1016/S1470-2045\(14\)70460-7](https://doi.org/10.1016/S1470-2045(14)70460-7).
 35. Bernet L, Pinero A, Martinez M, Vidal Sicart S, Algara M, Palomares E, et al. Consensus of the Spanish Society of Breast Senology and Pathology (SESPM) on selective biopsy of the sentinel node (BSGC) and axylar management in breast cancer (2022) [in Spanish]. *Rev Senol Pathol Mamar.* 2022;35:243–59.
 36. Banys-Paluchowski M, Gasparri ML, de Boniface J, Gentilini O, Stickeler E, Hartmann S, et al. Surgical management of the axilla in clinically node-positive breast cancer patients converting to clinical node negativity through neoadjuvant chemotherapy: current status, knowledge gaps, and rationale for the EUBREAST-03 AXSANA Study. *Cancers (Basel).* 2021;13:1565. <https://doi.org/10.3390/cancers13071565>.
 37. Simons JM, van Nijnatten TJA, van der Pol CC, Luiten EJT, Koppert LB, Smidt ML. Diagnostic accuracy of different surgical procedures for axillary staging after neoadjuvant systemic therapy in node-positive breast cancer: a systematic review and meta-analysis. *Ann Surg.* 2019;269(3):432–42. <https://doi.org/10.1097/SLA.0000000000003075>.
 38. Shah C, Al-Hilli Z, Vicini F. Advances in breast cancer radiotherapy: implications for current and future practice. *JCO Oncol Pract.* 2021;17:697–706. <https://doi.org/10.1200/OP.21.00635>.
 39. Shah C, Bauer-Nilsen K, McNulty RH, Vicini F. Novel radiation therapy approaches for breast cancer treatment. *Semin Oncol.* 2020;47:209–16. <https://doi.org/10.1053/j.seminoncol.2020.05.003>.

40. Brunt AM, Haviland JS, Sydenham M, Agrawal RK, Algorafi H, Alhasso A, et al. Ten-year results of FAST: a randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. *J Clin Oncol*. 2020;38:3261–72. <https://doi.org/10.1200/JCO.19.02750>.
41. Murray Brunt A, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet*. 2020;395:1613–26. [https://doi.org/10.1016/S0140-6736\(20\)30932-6](https://doi.org/10.1016/S0140-6736(20)30932-6).
42. Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in early breast cancer. *N Engl J Med*. 2023;388:585–94. <https://doi.org/10.1056/NEJMoa2207586>.
43. Whelan TJ, Olivetto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med*. 2015;373:307–16. <https://doi.org/10.1056/NEJMoa1415340>.
44. Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh IT, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol*. 2010;11(1):55–65. [https://doi.org/10.1016/S1470-2045\(09\)70314-6](https://doi.org/10.1016/S1470-2045(09)70314-6).
45. Andre F, Ismaila N, Allison KH, Barlow WE, Collyar DE, Damodaran S, et al. Biomarkers for adjuvant endocrine and chemotherapy in early-stage breast cancer: ASCO guideline update. *J Clin Oncol*. 2022;40:1816–37. <https://doi.org/10.1200/JCO.22.00069>.
46. Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016;375(8):717–29. <https://doi.org/10.1056/NEJMoa1602253>.
47. Dubsy P, Brase JC, Jakesz R, Rudas M, Singer CF, Greil R, et al. The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients. *Br J Cancer*. 2013;109:2959–64. <https://doi.org/10.1038/bjc.2013.671>.
48. Laenkholm AV, Jensen MB, Eriksen JO, Rasmussen BB, Knoop AS, Buckingham W, et al. PAM50 risk of recurrence score predicts 10-year distant recurrence in a comprehensive Danish cohort of postmenopausal women allocated to 5 years of endocrine therapy for hormone receptor-positive early breast cancer. *J Clin Oncol*. 2018;36(8):735–40. <https://doi.org/10.1200/JCO.2017.74.6586>.
49. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*. 2004;351:2817–26. <https://doi.org/10.1056/NEJMoa041588>.
50. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol*. 2006;24:3726–34. <https://doi.org/10.1200/JCO.2005.04.7985>.
51. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med*. 2015;373:2005–14. <https://doi.org/10.1056/NEJMoa1510764>.
52. Gnant M, Filipits M, Greil R, Stoeger H, Rudas M, Bago-Horvath Z, et al. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 risk of recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. *Ann Oncol*. 2014;25(2):339–45. <https://doi.org/10.1093/annonc/mdt494>.
53. Smith I, Robertson J, Kilburn L, Wilcox M, Evans A, Holcombe C, et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. *Lancet Oncol*. 2020;21(11):1443–54. [https://doi.org/10.1016/S1470-2045\(20\)30458-7](https://doi.org/10.1016/S1470-2045(20)30458-7).
54. Gluz O, Christgen M, Nitz U, Kuemmel S, Braun M, Thill M, et al. Impact of age and ovarian function suppression (OFS) on endocrine response to short preoperative endocrine therapy (ET): results from the multicenter ADAPTcycle trial (n = 4,334) [abstract LB01–05]. *Cancer Res*. 2024. <https://doi.org/10.1158/1538-7445.SABCS23-LB01-05>.
55. Nitz UA, Gluz O, Kummel S, Christgen M, Braun M, Aktas B, et al. Endocrine therapy response and 21-gene expression assay for therapy guidance in HR+/HER2- early breast cancer. *J Clin Oncol*. 2022;40:2557–67. <https://doi.org/10.1200/JCO.21.02759>.
56. Early Breast Cancer Trialists' Collaborative Group. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386:1341–52. [https://doi.org/10.1016/S0140-6736\(15\)61074-1](https://doi.org/10.1016/S0140-6736(15)61074-1).
57. Lohrisch C, Paltiel C, Gelmon K, Speers C, Taylor S, Barnett J, et al. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol*. 2006;24:4888–94. <https://doi.org/10.1200/JCO.2005.01.6089>.
58. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365:1687–717. [https://doi.org/10.1016/S0140-6736\(05\)66544-0](https://doi.org/10.1016/S0140-6736(05)66544-0).
59. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*. 2013;381:805–16. [https://doi.org/10.1016/S0140-6736\(12\)61963-1](https://doi.org/10.1016/S0140-6736(12)61963-1).
60. Gray RG, Rea D, Handley K, Bowden SJ, Perry P, Earl HM, et al. aTTom: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer [abstract]. *J Clin Oncol*. 2013. https://doi.org/10.1200/jco.2013.31.18_suppl.5.
61. Francis PA, Pagani O, Fleming GF, Walley BA, Colleoni M, Lang I, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med*. 2018;379(2):122–37. <https://doi.org/10.1056/NEJMoa1803164>.
62. LHRH-agonists in Early Breast Cancer Overview Group, Cuzick J, Ambrosi L, Davidson N, Jakesz R, Kaufmann M, et al. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet*. 2007;369:1711–23. [https://doi.org/10.1016/S0140-6736\(07\)60778-8](https://doi.org/10.1016/S0140-6736(07)60778-8).
63. BIG 1-98 Collaborative Group, Mouridsen H, Giobbie-Hurder A, Goldhirsch A, Thurlimann B, Paridaens R, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. *N Engl J Med*. 2009;361:766–76. <https://doi.org/10.1056/NEJMoa0810818>.
64. Boccardo F, Rubagotti A, Puntoni M, Guglielmini P, Amoroso D, Fini A, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. *J Clin Oncol*. 2005;23:5138–47. <https://doi.org/10.1200/JCO.2005.04.120>.

65. Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med*. 2004;350:1081–92. <https://doi.org/10.1056/NEJMoa040331>.
66. Derks MGM, Blok EJ, Seynaeve C, Nortier JWR, Kranenbarg EM, Liefers GJ, et al. Adjuvant tamoxifen and exemestane in women with postmenopausal early breast cancer (TEAM): 10-year follow-up of a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;18:1211–20. [https://doi.org/10.1016/S1470-2045\(17\)30419-9](https://doi.org/10.1016/S1470-2045(17)30419-9).
67. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet*. 2005;365:60–2. [https://doi.org/10.1016/S0140-6736\(04\)17666-6](https://doi.org/10.1016/S0140-6736(04)17666-6).
68. Jakesz R, Jonat W, Gnant M, Mittlboeck M, Greil R, Tausch C, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet*. 2005;366:455–62. [https://doi.org/10.1016/S0140-6736\(05\)67059-6](https://doi.org/10.1016/S0140-6736(05)67059-6).
69. Corona SP, Roviello G, Strina C, Milani M, Madaro S, Zanoni D, et al. Efficacy of extended aromatase inhibitors for hormone-receptor-positive breast cancer: a literature-based meta-analysis of randomized trials. *Breast*. 2019;46:19–24. <https://doi.org/10.1016/j.breast.2019.04.004>.
70. Bartlett JMS, Sgroi DC, Treuner K, Zhang Y, Ahmed I, Piper T, et al. Breast Cancer Index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen-To Offer More? (aTTom) trial. *Ann Oncol*. 2019;30(11):1776–83. <https://doi.org/10.1093/annonc/mdz289>.
71. Sgroi DC, Sestak I, Cuzick J, Zhang Y, Schnabel CA, Schroeder B, et al. Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. *Lancet Oncol*. 2013;14:1067–76. [https://doi.org/10.1016/S1470-2045\(13\)70387-5](https://doi.org/10.1016/S1470-2045(13)70387-5).
72. Zhang Y, Schroeder BE, Jerevall PL, Ly A, Nolan H, Schnabel CA, et al. A novel Breast Cancer Index for prediction of distant recurrence in HR(+) early-stage breast cancer with one to three positive nodes. *Clin Cancer Res*. 2017;23:7217–24. <https://doi.org/10.1158/1078-0432.CCR-17-1688>.
73. Dhesy-Thind S, Fletcher GG, Blanchette PS, Clemons MJ, Dillmon MS, Frank ES, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: a Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2017;35:2062–81. <https://doi.org/10.1200/JCO.2016.70.7257>.
74. Eisen A, Somerfield MR, Accordino MK, Blanchette PS, Clemons MJ, Dhesy-Thind S, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: ASCO-OH (CCO) Guideline Update. *J Clin Oncol*. 2022;40:787–800. <https://doi.org/10.1200/JCO.21.02647>.
75. Coleman R. Metastasis prevention with bone-targeted agents: a complex interaction between the microenvironment and tumour biology. *J Bone Miner Metab*. 2023;41(3):290–300. <https://doi.org/10.1007/s00774-023-01434-x>.
76. Coleman R, Hall A, Albanell J, Hanby A, Bell R, Cameron D, et al. Effect of MAF amplification on treatment outcomes with adjuvant zoledronic acid in early breast cancer: a secondary analysis of the international, open-label, randomised, controlled, phase 3 AZURE (BIG 01/04) trial. *Lancet Oncol*. 2017;18:1543–52. [https://doi.org/10.1016/S1470-2045\(17\)30603-4](https://doi.org/10.1016/S1470-2045(17)30603-4).
77. Paterson AHG, Lucas PC, Anderson SJ, Mamounas EP, Brufsky A, Baez-Diaz L, et al. MAF amplification and adjuvant clodronate outcomes in early-stage breast cancer in NSABP B-34 and potential impact on clinical practice. *JNCI Cancer Spectr*. 2021. <https://doi.org/10.1093/jncics/pkab054>.
78. Rastogi P, O'Shaughnessy J, Martin M, Boyle F, Cortes J, Rugo HS, et al. Adjuvant abemaciclib plus endocrine therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative, high-risk early breast cancer: results from a pre-planned monarchE overall survival interim analysis, including 5-year efficacy outcomes. *J Clin Oncol*. 2024;42:987–93. <https://doi.org/10.1200/JCO.23.01994>.
79. Fasching PA, Stroyakovskiy D, Yardley D, Huang C-S, Crown JP, Bardia E, et al. Adjuvant ribociclib (RIB) plus nonsteroidal aromatase inhibitor (NSAI) in patients (Pts) with HR+/HER2– early breast cancer (EBC): 4-year outcomes from the NATALEE trial [abstract LBA13]. *Ann Oncol*. 2024;35:e253700.
80. Geyer CE Jr, Garber JE, Gelber RD, Yothers G, Taboada M, Ross L, et al. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. *Ann Oncol*. 2022;33:1250–68. <https://doi.org/10.1016/j.annonc.2022.09.159>.
81. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. *N Engl J Med*. 2021;384:2394–405. <https://doi.org/10.1056/NEJMoa2105215>.
82. Kalinsky K, Barlow WE, Pathak HB, Gralow JR, Albain KS, Hayes DF, et al. Correlation of serum anti-Müllerian hormone (AMH) levels on identification of premenopausal patients (pts) with hormone receptor positive (HR+), HER2-negative, node-positive breast cancer most likely to benefit from adjuvant chemotherapy in SWOG S1007 (RxPONDER) [abstract 505]. *J Clin Oncol*. 2024;42:505.
83. Curigliano G, Burstein HJ, Winer EP, Gnant M, Dubsy P, Loibl S, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. *Ann Oncol*. 2017;28(8):1700–12. <https://doi.org/10.1093/annonc/mdx308>.
84. Nitz U, Gluz O, Huober J, Kreipe HH, Kates RE, Hartmann A, et al. Final analysis of the prospective WSG-AGO EC-Doc versus FEC phase III trial in intermediate-risk (pN1) early breast cancer: efficacy and predictive value of Ki67 expression. *Ann Oncol*. 2017;28:2899. <https://doi.org/10.1093/annonc/mdw349>.
85. Early Breast Cancer Trialists' Collaborative Group. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. *Lancet*. 2019;393:1440–52. [https://doi.org/10.1016/S0140-6736\(18\)33137-4](https://doi.org/10.1016/S0140-6736(18)33137-4).
86. Early Breast Cancer Trialists' Collaborative Group, Peto R, Davies C, Godwin J, Gray R, Pan HC, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet*. 2012;379:432–44. [https://doi.org/10.1016/S0140-6736\(11\)61625-5](https://doi.org/10.1016/S0140-6736(11)61625-5).
87. Geyer CE Jr, Bandos H, Rastogi P, Jacobs SA, Robidoux A, Fehrenbacher L, et al. Definitive results of a phase III adjuvant trial comparing six cycles of FEC-100 to four cycles of AC in women with operable node-negative breast cancer: the NSABP B-36 trial (NRG Oncology). *Breast Cancer Res Treat*. 2022;193(3):555–64. <https://doi.org/10.1007/s10549-021-06417-y>.
88. Jones S, Holmes FA, O'Shaughnessy J, Blum JL, Vukelja SJ, McIntyre KJ, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with

- doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. *J Clin Oncol.* 2009;27:1177–83. <https://doi.org/10.1200/JCO.2008.18.4028>.
89. Eggemann H, Ignatov A, Smith BJ, Altmann U, von Minckwitz G, Rohl FW, et al. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. *Breast Cancer Res Treat.* 2013;137(2):465–70. <https://doi.org/10.1007/s10549-012-2355-3>.
 90. Korde LA, Zujewski JA, Kamin L, Giordano S, Domchek S, Anderson WF, et al. Multidisciplinary meeting on male breast cancer: summary and research recommendations. *J Clin Oncol.* 2010;28:2114–22. <https://doi.org/10.1200/JCO.2009.25.5729>.
 91. Sousa B, Moser E, Cardoso F. An update on male breast cancer and future directions for research and treatment. *Eur J Pharmacol.* 2013;717:71–83. <https://doi.org/10.1016/j.ejphar.2013.03.037>.
 92. Gianni L, Baselga J, Eiermann W, Porta VG, Semiglazov V, Lluch A, et al. Phase III trial evaluating the addition of paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate, and fluorouracil, as adjuvant or primary systemic therapy: European Cooperative Trial in Operable Breast Cancer. *J Clin Oncol.* 2009;27:2474–81. <https://doi.org/10.1200/JCO.2008.19.2567>.
 93. Dowsett M, Ellis MJ, Dixon JM, Gluz O, Robertson J, Kates R, et al. Evidence-based guidelines for managing patients with primary ER+ HER2- breast cancer deferred from surgery due to the COVID-19 pandemic. *NPJ Breast Cancer.* 2020;6(1):21. <https://doi.org/10.1038/s41523-020-0168-9>.
 94. Smith IE, Dowsett M, Ebbs SR, Dixon JM, Skene A, Blohmer JU, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. *J Clin Oncol.* 2005;23:5108–16. <https://doi.org/10.1200/JCO.2005.04.005>.
 95. Masuda N, Sagara Y, Kinoshita T, Iwata H, Nakamura S, Yanagita Y, et al. Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial. *Lancet Oncol.* 2012;13(4):345–52. [https://doi.org/10.1016/S1470-2045\(11\)70373-4](https://doi.org/10.1016/S1470-2045(11)70373-4).
 96. Alba E, Calvo L, Albanell J, De la Haba JR, Arcusa Lanza A, Chacon JJ, et al. Chemotherapy (CT) and hormone therapy (HT) as neoadjuvant treatment in luminal breast cancer patients: results from the GEICAM/2006–03, a multicenter, randomized, phase-II study. *Ann Oncol.* 2012;23:3069–74. <https://doi.org/10.1093/annonc/mds132>.
 97. Ellis MJ, Suman VJ, Hoog J, Lin L, Snider J, Prat A, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype—ACOSOG Z1031. *J Clin Oncol.* 2011;29:2342–9. <https://doi.org/10.1200/JCO.2010.31.6950>.
 98. Prat A, Galvan P, Jimenez B, Buckingham W, Jeiranian HA, Schaper C, et al. Prediction of response to neoadjuvant chemotherapy using core needle biopsy samples with the Prosigna assay. *Clin Cancer Res.* 2016;22:560–6. <https://doi.org/10.1158/1078-0432.CCR-15-0630>.
 99. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet.* 2014;384:164–72. [https://doi.org/10.1016/S0140-6736\(13\)62422-8](https://doi.org/10.1016/S0140-6736(13)62422-8).
 100. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multi-centre, open-label, phase 2 trial. *Lancet Oncol.* 2012;13(1):25–32. [https://doi.org/10.1016/S1470-2045\(11\)70336-9](https://doi.org/10.1016/S1470-2045(11)70336-9).
 101. Loibl S, Piccart M, Clark E, Viale G, Caballero C, Henry C, et al. Adjuvant pertuzumab or placebo + trastuzumab + chemotherapy (P or Pla + T + CT) in patients (pts) with early HER2-positive operable breast cancer in APHINITY: final analysis at 11.3 years' median follow-up [abstract LBA1]. *EMSO Open.* 2025;10:1.
 102. van der Voort A, van Ramshorst MS, van Werkhoven ED, Mandjes IA, Kemper I, Vulink AJ, et al. Three-year follow-up of neoadjuvant chemotherapy with or without anthracyclines in the presence of dual ERBB2 blockade in patients with ERBB2-positive breast cancer: a secondary analysis of the TRAIN-2 Randomized, phase 3 trial. *JAMA Oncol.* 2021;7:978–84. <https://doi.org/10.1001/jamaoncol.2021.1371>.
 103. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol.* 2013;24:2278–84. <https://doi.org/10.1093/annonc/mdt182>.
 104. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med.* 2011;365(14):1273–83. <https://doi.org/10.1056/NEJMoa0910383>.
 105. Villacampa G, Pascual T, Tarantino P, Cortés J, Perez-García J, Llombart-Cussac A, et al. HER2DX and survival outcomes in early-stage HER2-positive breast cancer: an individual patient-level meta-analysis. *Lancet Oncol.* 2025;26:1100–12. [https://doi.org/10.1016/S1470-2045\(25\)00276-1](https://doi.org/10.1016/S1470-2045(25)00276-1).
 106. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet.* 2017;389:1195–205. [https://doi.org/10.1016/S0140-6736\(16\)32616-2](https://doi.org/10.1016/S0140-6736(16)32616-2).
 107. Perez EA, Romond EH, Suman VJ, Jeong JH, Sledge G, Geyer CE Jr, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol.* 2014;32:3744–52. <https://doi.org/10.1200/JCO.2014.55.5730>.
 108. Inno A, Barni S, Ghidini A, Zaniboni A, Petrelli F. One year versus a shorter duration of adjuvant trastuzumab for HER2-positive early breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat.* 2019;173(2):247–54. <https://doi.org/10.1007/s10549-018-5001-x>.
 109. Niraula S, Gyawali B. Optimal duration of adjuvant trastuzumab in treatment of early breast cancer: a meta-analysis of randomized controlled trials. *Breast Cancer Res Treat.* 2019;173(1):103–9. <https://doi.org/10.1007/s10549-018-4967-8>.
 110. Loibl S, Jassem J, Sonnenblick A, Parlier D, Winer E, Bergh J, et al. Adjuvant pertuzumab and trastuzumab in early human epidermal growth factor receptor 2-positive breast cancer in the APHINITY trial: third interim overall survival analysis with efficacy update. *J Clin Oncol.* 2024;42:3643–51. <https://doi.org/10.1200/JCO.23.02505>.
 111. Chan A, Moy B, Mansi J, Ejlersten B, Holmes FA, Chia S, et al. Final efficacy results of neratinib in HER2-positive hormone receptor-positive early-stage breast cancer from the phase III ExteNET trial. *Clin Breast Cancer.* 2021;21(1):80–91 e7. <https://doi.org/10.1016/j.clbc.2020.09.014>.

112. Loibl S, Mano M, Untch M, Huang C-S, Mamounas E, Wolmark N, et al. Phase III study of adjuvant ado-trastuzumab emtansine vs trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy: KATHERINE final IDFS and updated OS analysis [abstract GS03–12]. *Cancer Res.* 2024. <https://doi.org/10.1158/1538-7445.SABCS23-GS03-12>.
113. Piccart M, Procter M, Fumagalli D, de Azambuja E, Clark E, Ewer MS, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer in the APHINITY trial: 6 years' follow-up. *J Clin Oncol.* 2021;39:1448–57. <https://doi.org/10.1200/JCO.20.01204>.
114. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. *Nature.* 2000;406:747–52. <https://doi.org/10.1038/35021093>.
115. Vagia E, Mahalingam D, Cristofanilli M. The landscape of targeted therapies in TNBC. *Cancers (Basel).* 2020;12(4):916. <https://doi.org/10.3390/cancers12040916>.
116. An X, Lei X, Huang R, Luo R, Li H, Xu F, et al. Adjuvant chemotherapy for small, lymph node-negative, triple-negative breast cancer: a single-center study and a meta-analysis of the published literature. *Cancer.* 2020;126(16):3837–46. <https://doi.org/10.1002/cncr.32878>.
117. Mason SR, Willson ML, Egger SJ, Beith J, Dear RF, Goodwin A. Platinum-based chemotherapy for early triple-negative breast cancer. *Cochrane Database Syst Rev.* 2023;9(9):CD014805. <https://doi.org/10.1002/14651858.CD014805.pub2>.
118. Yu K-D, Ye F-G, He M, Fan L, Ma D, Mo M, et al. Effect of adjuvant paclitaxel and carboplatin on survival in women with triple-negative breast cancer: a phase 3 randomized clinical trial. *JAMA Oncol.* 2020;6:1390–6. <https://doi.org/10.1001/jamaoncol.2020.2965>.
119. Gao G, Wang Z, Qu X, Zhang Z. Prognostic value of tumor-infiltrating lymphocytes in patients with triple-negative breast cancer: a systematic review and meta-analysis. *BMC Cancer.* 2020;20:179. <https://doi.org/10.1186/s12885-020-6668-z>.
120. Loibl S, Andre F, Bachelot T, Barrios CH, Bergh J, Burstein HJ, et al. Early breast cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol.* 2024;35(2):159–82. <https://doi.org/10.1016/j.annonc.2023.11.016>.
121. Poggio F, Bruzzone M, Ceppi M, Ponde NF, La Valle G, Del Mastro L, et al. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis. *Ann Oncol.* 2018;29(7):1497–508. <https://doi.org/10.1093/annonc/mdy127>.
122. Schmid P, Cortes J, Dent R, McArthur H, Pusztai L, Kummel S, et al. Overall survival with pembrolizumab in early-stage triple-negative breast cancer. *N Engl J Med.* 2024;391:1981–91. <https://doi.org/10.1056/NEJMoa2409932>.
123. Schmid P, Cortes J, Dent RA, Pusztai L, McArthur H, Kummel S, et al. Pembrolizumab or placebo plus chemotherapy followed by pembrolizumab or placebo for early-stage TNBC: Updated EFS results from the phase III KEYNOTE-522 study [abstract LBA18]. *Ann Oncol.* 2023;34:S1257.
124. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med.* 2017;376:2147–59. <https://doi.org/10.1056/NEJMoa1612645>.
125. van Mackelenbergh MT, Seither F, Mobus V, O'Shaughnessy J, Martin M, Joensuu H, et al. Effects of capecitabine as part of neo-/adjuvant chemotherapy—a meta-analysis of individual breast cancer patient data from 13 randomised trials including 15,993 patients. *Eur J Cancer.* 2022;166:185–201. <https://doi.org/10.1016/j.ejca.2022.02.003>.
126. Barnadas A, Algara M, Cordoba O, Casas A, Gonzalez M, Marzo M, et al. Recommendations for the follow-up care of female breast cancer survivors: a guideline of the Spanish Society of Medical Oncology (SEOM), Spanish Society of General Medicine (SEMERGEN), Spanish Society for Family and Community Medicine (SEMFYC), Spanish Society for General and Family Physicians (SEMG), Spanish Society of Obstetrics and Gynecology (SEGO), Spanish Society of Radiation Oncology (SEOR), Spanish Society of Senology and Breast Pathology (SESPM), and Spanish Society of Cardiology (SEC). *Clin Transl Oncol.* 2018;20(6):687–94. <https://doi.org/10.1007/s12094-017-1801-4>.
127. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2019;30:1194–220. <https://doi.org/10.1093/annonc/mdz173>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.