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Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up[†]

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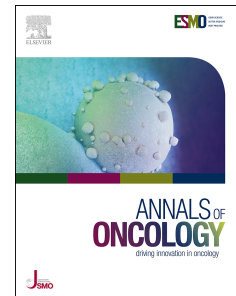
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Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up[†]

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Highlights (online only; up to 5 bullets, 125 characters per bullet including spaces):

- This ESMO Clinical Practice Guideline provides key recommendations and algorithms for the management of patients with EBC.
- It covers diagnosis, staging, risk assessment, treatment, follow-up, specific situations and the patient perspective.
- The author group is multidisciplinary, with experts representing a range of institutions worldwide.

- Recommendations, including ESMO-MCBS and ESCAT scores where applicable, are based on available evidence and expert opinion.
- Patient communication and shared decision making are covered with respect to diagnostic procedures and treatment options.

INCIDENCE AND EPIDEMIOLOGY

Global estimates indicated 2.3 million new cases of breast cancer in 2020, contributing to nearly 12% of all new cancer cases, with 685,000 deaths in the same year.¹ Breast cancer detection has increased due to improvements in screening techniques. The mortality rate has decreased in recent years in Western populations, especially in younger age groups^{2,3}, but breast cancer is still the leading cause of cancer-related deaths for women worldwide. Most early breast cancer (EBC) cases can be cured by multimodality treatment, although cure rates vary by clinical stage and subtype.

SCREENING, DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Breast cancer screening

Details on screening are covered in the **Supplementary Material Section 1**, available at *Annals of Oncology* online, and are also described in the ESMO Clinical Practice Guideline (CPG) for risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes.⁴

Diagnosis and imaging

Diagnosis and imaging are described in the **Supplementary Material Section 2**, available at *Annals of Oncology* online. **Figure 1** shows a proposed algorithm for the diagnostic work-up and staging of EBC.

Hereditary breast cancer

Details on hereditary breast cancer are covered in the **Supplementary Material Section 3**, available at *Annals of Oncology* online.

Histomorphological assessment, biomarkers and molecular pathology

Histomorphological assessment, biomarkers and molecular pathology are described in the **Supplementary Material Section 4** and **Supplementary Tables S1-S4**, available at *Annals of Oncology* online.

Recommendations

- Regular (every 2 years) mammography screening is recommended in average-risk women 50-69 years of age [I, A]. Regular mammography may also be carried out in women 45-49 and 70-74 years, although there is less evidence of benefit [I, B].
- Screening in women with a strong family history or known germline *BRCA1/2* and other high-risk pathogenic variants (PVs) should follow the ESMO CPG for risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes [III, A].
- Further diagnostic work-up is based on clinical examination and imaging, including bilateral mammography and ultrasound (US) of both breasts and regional lymph nodes (LNs) or two-dimensional digital mammography in the symptomatic setting [I, A].
- Digital breast tomosynthesis (with or without synthetic mammography) and contrast-enhanced mammography can be considered as alternatives, where available and appropriate [II, B].
- Magnetic resonance imaging (MRI) of the breasts is recommended in case of uncertainties following standard imaging and in special clinical situations (e.g. familial breast cancer associated with germline *BRCA1/2* mutations (*gBRCA1/2m*) and other high-risk PVs, lobular cancers, suspicion of multifocality and/or multicentricity, presence of breast implants) [I, A].
- Assessment of distant metastases (bone, liver and lung) is recommended only in patients with stage IIb and higher disease (especially with extended LN involvement), patients with a high risk of recurrence at first diagnosis and/or in symptomatic patients [III, A].
- Pretreatment pathological assessment, including a complete histomorphological, immunohistochemical and molecular assessment, if applicable, is recommended at the time of diagnosis and should include primary tumour histology and axillary node histology/cytology (if node involvement is suspected clinically) [I, A].
- Assessment should include histological type, grade and immunohistochemistry (IHC) evaluation of estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) biomarkers and a

proliferation marker such as Ki-67 [I, A]. FISH testing should be carried out in cases of an equivocal HER2 IHC score (HER2 2+) [I, A; ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) score: I-A].

- Tumours should be grouped into biological subtypes, defined by routine histology and IHC results, as luminal A-like, luminal B-like, HER2-positive and triple-negative [I, A]. **Supplementary Material Section 4**, available at *Annals of Oncology* online, provides details on subtype classification.
- In cases of hormone receptor (HR)-positive, HER2-negative EBC with uncertainty about indications for adjuvant chemotherapy (ChT) (after consideration of all clinical and pathological factors), gene expression assays and endocrine response assessment in the preoperative setting can be used [II, B].
- Tumour-infiltrating lymphocytes (TILs) may add prognostic and predictive information, particularly in triple-negative breast cancer (TNBC) and HER2-positive breast cancer, but there are no distinct TIL thresholds for treatment decisions [I, B].
- Programmed death-ligand 1 (PD-L1) expression levels **should not** be used to guide treatment decisions in EBC [I, E].
- Germline testing and subsequent genetic counselling for PVs in *BRCA1/2* should be offered to patients who meet the respective national criteria and to those who are candidates for adjuvant olaparib therapy [I, A; ESCAT score I-A].

STAGING AND RISK ASSESSMENT

Summary details on staging and risk assessment are included in the **Supplementary Material Section 5** and in **Supplementary Tables S2-S4**, available at *Annals of Oncology* online.

Recommendations

- Disease stage and final pathological assessment of surgical specimens should be made according to the World Health Organization classification of tumours

and the eighth edition of the Union for International Cancer Control tumour–node–metastasis (TNM) staging system [V, A].

- Minimum blood work-up (a full blood count, liver and renal function tests, alkaline phosphatase and calcium levels) is recommended before surgery and systemic (neo)adjuvant therapy [V, A].
- A computed tomography (CT) scan of the chest, abdominal imaging (US, CT or MRI scan) and a bone scan can be considered for patients with:
 - clinically positive axillary nodes
 - large tumours (e.g. 5 cm)
 - aggressive biology
 - clinical signs, symptoms or laboratory values suggesting the presence of metastases [III, A]
- The complete medical and family history must be evaluated, including menopausal status (if in doubt, serum estradiol and follicle-stimulating hormone levels should be measured) [V, A].
- [¹⁸F]2-fluoro-2-deoxy-D-glucose (FDG)–positron emission tomography (PET)–CT scanning may be used instead of CT and bone scintigraphy particularly for high-risk patients and when conventional methods are inconclusive [II, B].

MANAGEMENT OF EBC

General treatment principles

The recommendations in this guideline provide a framework to promote optimal patient care. However, treatment decisions for each patient should be based on an individual risk–benefit analysis considering patient/disease characteristics, comorbidities and patient preferences. All treatment decisions should be made as part of a shared decision-making process with the patient. Clinical trial participation is preferred whenever available.

Supplementary Material Section 6, available at *Annals of Oncology* online, provides further details on general treatment principles.

For a general overview of EBC management, see **Figure 2**.

Patient communication and shared decision making

Supplementary Material Section 7, available at *Annals of Oncology* online, provides details on patient communication and shared decision making.

Locoregional treatment

Surgery. Breast-conserving surgery (BCS) is an appropriate surgical option for most patients with breast cancer. For patients undergoing BCS, typically with post-operative radiotherapy (RT), also known as breast-conserving therapy (BCT), optimal oncological and cosmetic outcomes are important. It is, therefore, recommended that breast surgeons should either work with plastic surgeons or be trained in oncoplastic approaches themselves. Shared decision making should be facilitated using appropriate patient-oriented information tools.⁵

Margin status should be reported; for invasive cancer, no tumour at the inked margin is required; for *in situ* disease, ≥ 2 mm is preferred.⁶

Marking the tumour bed with clips facilitates an accurate planning of either the radiation boost field or for partial breast irradiation, if indicated.⁷ The aim should be to achieve local recurrence rates of $<0.5\%$ per year and $\leq 5\%$ overall per 5 years. Nipple-sparing mastectomy (NSM) and skin-sparing mastectomy (SSM) are generally considered oncologically safe while improving cosmetic outcomes for cases where primary breast conservation cannot be achieved.

Immediate or delayed breast reconstruction should be offered to most women requiring mastectomy. Oncological reasons to advise against immediate reconstruction include inflammatory breast cancer or situations where the risk of locoregional recurrence is high to avoid delays in initiating post-operative RT.⁸ Autologous tissue-based reconstructive techniques generally tolerate post-operative RT better than implant-based reconstruction, both preceding and following post-mastectomy RT (PMRT).⁹

For breast reconstruction, many immediate or delayed surgical options are available. Silicone gel implants are generally safe, but patients should be informed about the small risk of anaplastic large-cell lymphoma with certain implants.¹⁰

The optimal reconstruction technique should be discussed individually, considering anatomical, treatment- and patient-related factors and preferences.

Advances in management of axillary LNs. See **Figure 3** for a treatment algorithm on the management of axillary LN (ALN) involvement with primary surgery or primary systemic/neoadjuvant therapy.

Regional LN status remains one of the strongest prognosticators of long-term outcome in EBC. Sentinel LN biopsy (SLNB) is the standard staging approach for clinically negative ALNs at diagnosis or after neoadjuvant ChT. SLNB is associated with less shoulder stiffness, pain and arm swelling morbidity than complete ALN dissection (ALND). With appropriate training, high identification rates ($\geq 97\%$), low false-negative rates and favourable ALN recurrence rates following SLNB are achievable.¹¹ Notably, isolated ALN recurrence occurs in $<1\%$ of negative SLNBs despite a false-negative rate of 5%-10%.¹²

Micrometastases (0.2-2.0 mm) (N1mic) or isolated tumour cells (N0itc+) in treatment-naïve ALNs are prognostically equivalent to N0 disease, with local and systemic treatment options selected based on other tumour- and patient-based parameters. Based on the IBCSG 23-01 trial, further ALN treatment is not required if a sentinel LN (SLN) has micrometastases unless neoadjuvant therapy was given.¹³ Routine IHC or PCR for the evaluation of SLNs in patients unexposed to neoadjuvant ChT is therefore not recommended.¹⁴

Micrometastases after neoadjuvant ChT indicate a non-pathological complete response (pCR) which is associated with worse prognosis than micrometastases in treatment-naïve LNs.¹⁵

For cases with macrometastatic spread to the SLN, the ACOSOG Z0011 trial reported similar outcomes without ALND for patients with clinical T1-T2 cN0 invasive breast cancer who had 1-2 SLNs containing metastases but no gross extracapsular extension (treated with BCS, tangential post-operative RT including part of the axilla and adjuvant systemic therapy).¹² For patients who do not meet these criteria, and for patients with more than two positive SLNs, ALND remains the standard of care. Another option for patients with cN0 disease and SLN metastases is axillary RT, as demonstrated by the AMAROS and OTOASOR studies.^{16,17} Nodal involvement-based indications for systemic therapy options (e.g. abemaciclib, olaparib) need to be considered by a multidisciplinary team (MDT) when choosing between ALND or

RT in case of positive SLNs. The question of whether patients who have undergone mastectomy with or without an indication for PMRT (low-risk tumours, T <5 cm) can forego ALND after positive SLNB remains unresolved.¹⁸ The benefit of ALND in patients with micrometastatic and macrometastatic SLNs after neoadjuvant ChT is currently being investigated. Thus, until outcomes are reported from randomised trials, ALND is recommended for ypN1mi as well as any macrometastatic disease (ypN+) regardless of other features. There are currently no available data on isolated tumour cells in ALND after neoadjuvant ChT.

Occult breast cancer presents as regional LN metastases without an identifiable primary lesion within the breast. It constitutes <0.5% of all new breast cancer cases. Routine diagnosis requires breast MRI and systemic staging, preferably by FDG–PET–CT. ALND with whole-breast RT (WBRT) and regional RT is the preferred treatment. Systemic therapy, including neoadjuvant therapy, should be according to recommendations by subtype and stage.¹⁹

Surgery after primary systemic/neoadjuvant therapy. Before primary systemic therapy (PST), it is recommended to mark the primary site (using a marker clip or carbon localisation) to facilitate accurate surgery when BCS is anticipated. In case of a positive ALN (cN1), marking the positive LN will allow ALND to be avoided for patients who are cN0 after PST. Although not mandatory, breast MRI is the most accurate modality for assessing the extent of residual disease following PST but only when coupled with pretreatment baseline MRI.

After PST, breast surgery must follow the same principles of oncological safety, low morbidity and good cosmesis as primary breast surgery. Downsizing of a large unifocal primary tumour with PST will allow BCS in a substantial proportion of patients. Even in cases with multifocal disease or when tumour shrinkage is limited, patients may still be eligible for BCS. Surgery following PST should usually be planned according to the new tumour extent and not the original tumour bed.²⁰

In patients with clinically- and imaging-negative axilla, SLNB after PST is the method of choice. In patients with biopsy-proven limited initial nodal involvement (pN1) who convert to clinically negative (ycN0), SLNB can be carried out safely, as shown by the results from the SENTINA, ACOSOG Z1071, SN FNAC and GANEA 2 trials.²¹⁻²⁴

In these studies, false-negative rates of SLN following PST ranged from 8% to 14%. False-negative rates can be decreased to <5% by marking the biopsied positive node(s) to verify their removal, as well as using a dual tracer and removing ≥ 3 SLNs—comparable to targeted axillary dissection (TAD) involving removal of the clipped node plus ≥ 1 SLN. According to current evidence, any tumour deposits in SLNs following PST prompt ALND. Furthermore, available data from trials do not support the routine use of SLNB in patients with initial bulky nodal involvement [cN2-3 (detected clinically or on PET-CT)] or in inflammatory breast cancer, even if converted to ycN0 after PST.

WBRT after BCS. WBRT after BCS results in an absolute reduction in the 10-year risk of any first recurrence (locoregional or distant) and the 15-year risk of breast cancer-related mortality of 15.7% and 3.8%, respectively.²⁵ Boost RT reduces local recurrence rates compared with no boost (relative reduction of 41% and 35% at 10 and 20 years, respectively) and is indicated for patients with unfavourable risk factors for local control.²⁶

Excellent results equivalent to WBRT are reported after accelerated partial breast irradiation (APBI) for well-selected patients with low-risk disease according to the ESTRO consensus recommendations.²⁷⁻²⁹ Low risk-features suitable for partial breast irradiation are: luminal-like subtypes small tumour (≤ 3 cm), absence of lymphovascular space invasion, non-lobular invasive carcinoma, tumour grade 1–2, low-to-intermediate grade ductal carcinoma *in situ* (DCIS) (sized ≤ 2.5 cm with clear surgical margins ≥ 3 mm), age at diagnosis ≥ 50 years, unicentric or unifocal lesion, clear surgical margins (> 2 mm), node negative (including isolated tumour cells) and no use of PST. Any technique, including external beam RT, brachytherapy, endocavitary and intraoperative RT with electrons techniques, allowing full coverage of the entire target volume, is suitable.^{28,30}

Omission of RT after BCS remains investigational. However, women at advanced age and/or with co-morbidities, who intend to take ≥ 5 years of adjuvant endocrine therapy (ET), may forego RT if they accept an increased risk for local recurrences especially at long term as well as the possible side-effects of the ET.

PMRT. For patients with node-positive disease, PMRT results in an absolute reduction in first recurrence of 10.6% at 10 years and an absolute reduction in breast cancer-related mortality of 8.1% at 20 years.³¹ PMRT is recommended for high-risk disease (including involved resection margins, ≥ 4 involved ALNs and T3-T4 tumours) independent of the nodal status. It should also be considered in patients with intermediate-risk features (e.g. lymphovascular invasion, age), including those with 1-3 positive ALNs.³¹

Regional RT. The use of comprehensive locoregional RT encompassing the chest wall and all regional LNs improves outcomes, especially for patients with ALN involvement. Modern locoregional RT, based on CT planned loco-regional targets, will result in reduced recurrence with the main effect being on distant recurrence. RT has been shown to significantly reduce breast cancer mortality [rate ratio 0.87, 95% confidence interval (CI) 0.80-0.94, $P = 0.0010$], with no significant effect on non-breast-cancer mortality (0.97, 0.84-1.11, $P = 0.63$), leading to significantly reduced all-cause mortality (0.90, 0.84-0.96, $P = 0.0022$).³²

In the case of PST, indications and target volumes can be individualised based on the clinical tumour stage combined with the tumour response. The European Society for Radiotherapy and Oncology (ESTRO) guidelines for target volume delineation in breast cancer precisely describe the LN location to be treated, specifying that in regionally advanced disease, individualisation is required.³³

After ALND, the resected part of the axilla should not be irradiated, except in cases of clear residual disease after surgery. After a positive SLNB without subsequent ALND, regional RT is advised, the extent being defined by other risk factors (e.g. lowest risk: no RT; intermediate risk: exclusive level 1-2 RT; highest risk: full level 1-4 RT including the internal mammary nodes).^{25,31,34}

RT and breast reconstruction. PMRT can be administered after immediate breast reconstruction. Better outcomes are usually obtained with autologous tissue reconstruction.⁹

RT doses and fractionation. Doses used for local and/or regional adjuvant irradiation have historically been 45-50 Gy in 25-28 fractions of 1.8-2.0 Gy with a

typical boost dose of 10-16 Gy in 2 Gy single doses. Moderate hypofractionation (e.g. 15-16 fractions of 2.50-2.67 Gy single dose) has shown equivalent effectiveness and comparable side-effects. The FAST-Forward trial demonstrated that after 6 years median follow-up, ultra-hypofractionation of 26 Gy in five fractions in one week results in the same oncological and safety outcomes for breast and chest wall irradiation.³⁵ In terms of outcomes after ultra-hypofractionation for locoregional RT, data from a prospective sub-study are awaited. The ESTRO Advisory Committee in Radiation Oncology Practice consensus recommends shorter regimens whenever indicated.²⁹ Another ultra-hypofractionation regimen using fraction sizes of 5.7-6.0 Gy, delivered once a week over 5 weeks, can be used for frail patients with difficulties of daily transportation.³⁶

(Neo)adjuvant systemic treatment

General aspects of systemic therapy. The decision regarding systemic treatment should be based on the opportunities for pathological response-guided post-operative systemic therapy and the benefit from its use as well as an individual's risk of relapse and predicted sensitivity to treatment types. The final decision should also incorporate the short- and long-term toxicities and the patient's biological age, general health status, comorbidities and preferences. Neoadjuvant therapy should start as soon as diagnosis and staging are completed (ideally within 2-4 weeks). Adjuvant systemic therapy should be started without undue delays (ideally within 4-6 weeks), as data show a decrease in efficacy when it is administered >12 weeks after surgery.³⁷ Whenever systemic adjuvant ChT is indicated, neoadjuvant use of the same regimen can also be considered. ET should be used in all patients with HR-positive breast cancer unless contraindicated.³⁸

HR-positive, HER2-negative EBC. **Figures 4-5** provide treatment algorithms and **Supplementary Table S5**, available at *Annals of Oncology* online, provides an overview of adjuvant therapy for patients with HR-positive, HER2-negative EBC.

HR-positive, HER2-negative tumours are the most common type of EBC, accounting for >70% of all cases worldwide. Risk factors for recurrence of HR-positive cancers are well established (see the 'Screening, diagnosis, pathology and molecular biology' section of this guideline).

Treatment is individualised based on tumour stage and biology [subtype (**Supplementary Material Section 4**, available at *Annals of Oncology* online, provides details on subtype classification)], menopausal status and the several classes of therapeutic interventions available, including ET, ChT and targeted therapy. Although the relative benefit of ChT and ET might be the same in different subgroups, the absolute benefit depends on the individual risk of recurrence. The absolute benefit should be considered in conjunction with the side-effects of each treatment in an informed decision-making process with the patient.

Anatomic risk variables (tumour size, nodal status) do not influence treatment sensitivity or the relative benefit from adjuvant therapy; however, by guiding therapy selection, they can have a major impact on absolute risk reduction. Higher-risk HR-positive tumours generally warrant aromatase inhibitor (AI)-based therapy, consideration of ChT, targeted treatments, extended adjuvant ET and, for premenopausal women, ovarian function suppression (OFS) and ChT.

For most HR-positive, HER2-negative, screening-detected breast cancer, surgery is the initial treatment modality. For women with larger tumours or clinical nodal involvement, neoadjuvant systemic therapy may be preferred. Neoadjuvant ChT can be effective for surgical downstaging of HR-positive, HER2-negative cancers; however, pCR is uncommon although it occurs more frequently in young patients and/or patients with high-grade tumours.³⁹ For selection of appropriate neoadjuvant treatments, similar considerations as for adjuvant therapy apply.

Adjuvant ChT reduces the relative recurrence risk and improves survival in women by 25%-30% irrespective of the subtype.⁴⁰⁻⁴⁴ Defining cohorts most appropriate for ChT increasingly depends on classifying tumours based on genomic signatures as well as other biological factors (i.e. ER, PgR, HER2 and Ki-67) that refine prognosis beyond pathology alone. The combination of low grade and/or low Ki-67 level with strong ER/PgR expression and endocrine response to a short course of preoperative ET may serve as surrogates for a sufficiently favourable biology.^{45,46} Among postmenopausal women with node-negative disease or with 1-3 positive nodes and low-risk genomic signature scores/low-risk biology, adjuvant ChT did not further reduce recurrence rates compared with ET alone.⁴⁷⁻⁴⁹ Among premenopausal women with node-negative disease or 1-3 positive nodes and low-risk genomic

signature scores, adjuvant ChT did reduce recurrence rates compared with ET alone.^{47,49} Some of this benefit may be due to ChT-induced amenorrhoea, though it is unclear precisely how much of the difference is accounted for by direct cytotoxicity against micrometastatic cancer versus secondary endocrine effects of ChT.

Endocrine response assessment using Ki-67 response ($Ki67 \leq 10\%$) after a 4-week preoperative ET regimen may be used to estimate benefit from adjuvant ChT in patients with 0-3 involved LNs, especially for postmenopausal women.^{45,46} For women with HR-positive, HER2-negative breast cancer warranting ChT, anthracycline, taxane and alkylator-based ChT regimens are standard but non-anthracycline-based regimens may be appropriate for stage I and II cancers with limited nodal involvement.

Adjuvant ET is almost universal for patients with HR-positive invasive breast cancer of any stage and HER2 status and reduces the risk of locoregional recurrence, distant metastatic recurrence and contralateral breast cancer, while improving overall survival (OS).^{50,51}

Among premenopausal women with higher-risk HR-positive cancers, OFS paired with an AI or tamoxifen reduces the likelihood of recurrence and improves OS versus tamoxifen alone. OFS with an AI reduces recurrences compared with OFS with tamoxifen.⁵¹ In postmenopausal women, AIs, used either upfront or sequentially after 2-3 years of tamoxifen, offer lower risk of recurrence compared with tamoxifen alone, especially in higher-stage cancers.⁵¹ Standard treatment duration is 5 years but extended durations to 7 or 10 years further lower recurrence risk and increase survival, particularly in higher-stage cancers.^{52,53}

The use of adjuvant bisphosphonate therapy in postmenopausal women with EBC, as well as premenopausal women receiving OFS, can lower the risk of tumour recurrence and mitigate the side-effects of osteopenia/osteoporosis seen with AIs. A meta-analysis published by The Early Breast Cancer Trialists' Collaborative Group indicates a benefit irrespective of the HR status and bisphosphonate type or regimen. Large randomised trials of adjuvant denosumab have had mixed results in terms of impact on breast cancer outcomes and it is therefore not recommended.^{54,55}

Targeted therapy with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in addition to ET has been widely studied in EBC. The addition of abemaciclib for 2 years reduced

the absolute risk of recurrence at 4 years by 6.4% [hazard ratio 0.664, 95% CI 0.578-0.762, $P < 0.0001$] in a cohort of women with HR-positive, HER2-negative breast cancer with either ≥ 4 involved LNs, 1-3 positive nodes with either T3 (> 5 cm) tumours or grade 3 histology or Ki-67 expression $\geq 20\%$.⁵⁶ The NATALEE trial evaluated the addition of ribociclib 400 mg/day (days 1-21 of every 28-day cycle) for 3 years to adjuvant ET in women with American Joint Committee on Cancer (eighth edition) stage II (either N0 with grade 2-3 and/or Ki67 $\geq 20\%$ or N1) or stage III HR-positive, HER2-negative breast cancer. It reached its primary endpoint with a 3.3% improvement in 3-year invasive disease-free survival (iDFS) (hazard ratio 0.748, 95% CI 0.618-0.906, $P = 0.0014$).⁵⁷ Pending approval by the Food and Drug Administration (FDA) or the European Medicines Agency (EMA), this could potentially be another option for intermediate and high-risk disease.

In patients with *gBRCA1/2m* and high-risk HER2-negative tumours, adjuvant olaparib for 1 year improves DFS (hazard ratio 0.63, 95% C) 0.5-0.78) and OS (hazard ratio 0.68, 95% CI 0.47-0.97, $P = 0.009$) irrespective of HR status. At 4 years, the absolute differences in iDFS and distant DFS were 7.3% (95% CI 3.0%-11.5%) and 7.4% (95% CI 3.6%-11.3%), respectively. Patients with HR-positive tumours had to have ≥ 4 involved LNs at diagnosis or a clinical and pathological stage plus ER and nuclear grade (CPS + EG) score ≥ 3 to be eligible for inclusion in the trial.⁵⁸

Though supportive interventions can reduce many therapy-related side-effects, considering the modest reductions in recurrence or improvement in OS with many common treatments for ER-positive breast cancer, especially in lower-risk tumours, patient preferences are an important part of the equation governing adjuvant treatment recommendations.

HER2-positive EBC. The addition of trastuzumab to ChT improves OS by approximately one third. The relative magnitude of the survival benefit for patients with HR-positive EBC is the same as for HR-negative EBC after 10 years of follow-up; however, the latter have earlier recurrences.⁵⁹ **Figure 6** provides a treatment algorithm for patients with HER2-positive EBC.

Neoadjuvant and post-neoadjuvant systemic treatment based on pCR. In patients with clinical stage II-III disease, the preferred option is initial preoperative systemic therapy followed by local therapy, with the aim of evaluating treatment efficacy by pathological response assessment, guiding risk stratification, reducing the extent of surgical need and determining the adjuvant treatment plan. Patients with a pCR after neoadjuvant treatment demonstrate a substantially lower risk of disease recurrence.³⁹ However, patients with a high initial tumour burden are still at elevated risk of relapse even with a pCR.^{60,61} The presence of residual invasive tumour in the breast or nodes indicate poorer outcomes.³⁹ Anthracycline–taxane-based combinations with HER2-targeted agents have been a backbone of (neo)adjuvant ChT in patients with HER2-positive disease⁶² but are associated with a very low, but potentially serious risk of cardiac toxicity and secondary acute myeloid leukaemia (one additional treatment-induced leukaemia per 400-500 patients).^{63,64} Anthracycline-free regimens comprising carboplatin with taxanes have been tested in phase II (PREDIX HER2, TRAIN2, TRYPHAENA) and III (BCIRG-006) clinical trials, reporting similar outcomes to anthracycline-containing regimens and improved cardiac safety.⁶⁵⁻⁶⁸ Neoadjuvant ChT combined with dual HER2 blockade [trastuzumab–pertuzumab (HP)] results in higher pCR rates compared with trastuzumab alone, translating into improved outcomes, particularly among patients with LN-positive cancers.⁶⁹ In low-to-intermediate-risk HER2-positive, HR-negative disease, 12 weeks of paclitaxel in combination with HP without post-operative anthracyclines showed a pCR rate of >90% and an iDFS at 5 years of ~98% in highly selected patients in a single arm phase II study.⁷⁰ This regimen is currently being evaluated in other optimisation trials.⁷¹

Patients with pCR after standard neoadjuvant systemic therapy should continue anti-HER2 therapy for a total duration of 1 year.⁷⁰ The phase III KATHERINE trial reported improved outcomes in patients who had residual invasive cancer and received adjuvant trastuzumab emtansine (T-DM1) instead of trastuzumab; the proportion of patients free of invasive disease at 3 years was 88.3% versus 77.0%, respectively.⁷² T-DM1 significantly decreased the risk of recurrence of invasive breast cancer or death (hazard ratio 0.50, 95% CI 0.39-0.64, $P < 0.001$). T-DM1 was effective irrespective of the HER2 status in the non-pCR specimen.⁷³ Adjuvant RT

and ET may safely be given concurrently with T-DM1 but data are limited for patients having extensive nodal irradiation including internal mammary nodes.⁷⁴ For patients with a pCR who were clinically node-negative at initial diagnosis, the addition of pertuzumab to trastuzumab should not be considered on a routine basis in the post-neoadjuvant treatment setting. There is potential benefit in patients who are suspected to have been node-positive at baseline (~30% of patients¹¹).⁷⁵

Adjuvant therapy for HER2-positive breast cancer. Patients with HER2-positive breast cancer treated with initial surgery should receive adjuvant treatment with HER2-directed therapy plus ChT and ET if HR-positive. ESCAT scores apply only in the case of HER2 gene amplification by FISH/CISH.

De-intensification of adjuvant treatment can be considered for pathological stage pT1 pN0 disease, using a regimen of weekly paclitaxel for up to 12 doses along with 12 months of trastuzumab. This de-intensified regimen provided low recurrence rates in a prospective single arm phase II trial, reporting 10-year iDFS, breast cancer-specific survival and OS rates of 91.3%, 98.8% and 94.3%, respectively.⁷⁶

The APHINITY trial compared adjuvant HP with trastuzumab–placebo, both in combination with anthracycline-based (78%) or non-anthracycline-based ChT. The initial report demonstrated that HP significantly improved 3-year iDFS (hazard ratio 0.81, 95% CI 0.66-1.00, $P = 0.045$).⁷⁷ With longer follow-up, the N+ subgroup maintained a clear iDFS benefit favouring HP, with an 8-year iDFS of 86% versus 81% (hazard ratio 0.72, 95% CI 0.60-0.87) without significantly improving OS; no benefit was seen in the node-negative subgroup.⁷⁵ The HR-positive cohort derived at least the same benefit as the HR-negative group.⁷⁵

Duration of adjuvant treatment with HER2-targeted therapy. The length of trastuzumab administration in the adjuvant setting has been established based on the results of pivotal trials, which have arbitrarily chosen a duration of 12 months.⁵⁹ The HERA trial reported no additional benefit from 2 years of treatment.⁷⁸ Clinical studies have investigated the non-inferiority of a shorter duration of trastuzumab of 6 months versus 12 months. The PERSEPHONE trial claimed non-inferiority for 6 months versus 12 months of trastuzumab treatment,⁷⁹ while others could not rule out non-inferiority.⁸⁰ While these results are considered inconclusive, the benefit of 12

months versus 6 months of trastuzumab may need to be balanced against the baseline risk of recurrence in resource-constrained settings with limited ability to provide 12 months of treatment.⁸¹ It remains unknown whether patients who achieve a complete response to neoadjuvant ChT plus HER2-targeted therapy need to complete 12 months of trastuzumab.

Tyrosine kinase inhibitors as adjuvant therapy. Adjuvant tyrosine kinase inhibitors (TKIs) have been evaluated in clinical trials in HER2-positive EBC. None of the trials evaluating lapatinib in EBC significantly improved outcomes. The phase III ExteNET trial evaluated 1 year of extended therapy with neratinib after completion of 1 year of adjuvant trastuzumab. This trial showed that neratinib significantly improved iDFS overall (hazard ratio 0.73, 95% CI 0.57-0.92, $P = 0.0083$) but largely in the subgroup of HR-positive tumours (hazard ratio 0.60, 95% CI 0.43-0.83, $P = 0.063$).^{82,83} The study was conducted before the advent of pertuzumab- or T-DM1-based therapies, which are now standard. Neratinib is associated with high rates of moderate to severe diarrhoea; however, implementation of a dose escalation schedule and optimisation of prophylactic interventions can result in lower grade 3 diarrhoea rates, better therapeutic adherence and lower discontinuation rates.⁸⁴

TNBC. **Figure 7** provides a treatment algorithm for patients with early TNBC.

Neoadjuvant ChT is the standard for T1c/N0 or greater TNBC. The majority of patients with pT1a pN0 disease do not benefit from adjuvant ChT while data on the efficacy of adjuvant ChT in pT1b pN0 are unclear. Patients with low-grade TNBC of specific histologies (e.g. adenoid cystic, secretory, medullary) seem to derive little or no benefit from adjuvant ChT, particularly in those with low-risk clinical features, although confidence in these results is limited by small numbers and the retrospective nature of the data.^{85,86}

The agents in the ChT regimens do not differ between neoadjuvant and adjuvant treatment other than the use of pembrolizumab in the neoadjuvant setting for high risk patients. However, neoadjuvant treatment allows pathological response-guided adjuvant treatment that can improve survival, and is therefore the preferred strategy. Evidence-based regimens without immune checkpoint inhibitors (ICIs) are sequential: anthracycline-based therapy followed by a taxane or taxane–carboplatin

or vice versa. The benefit from carboplatin is independent of *gBRCA1/2m* status.^{87,88} The standard anthracycline-based regimens are doxorubicin–cyclophosphamide (AC) or epirubicin–cyclophosphamide (EC) given for four cycles over 8 or 12 weeks followed by a taxane given for four cycles over 8 or 12 weeks. Dose-dense therapies, including dose-dense AC or EC and weekly paclitaxel, are preferred.⁴¹ Six cycles of a non-anthracycline, taxane-based regimen, such as docetaxel–cyclophosphamide or a taxane plus carboplatin, may be used as an alternative in patients for whom anthracyclines are contraindicated. Adding carboplatin to the taxane improves pCR rates and event-free survival (EFS) but its impact on OS is less certain. Patients with *gBRCA1/2m* respond very well to standard anthracycline–taxane-based ChT irrespective of platinum use. Single-agent poly (ADP-ribose) polymerase (PARP) inhibitors induce high (>40%) pCR rates, but are not considered standard of care as neoadjuvant therapy and may be best reserved for adjuvant therapy for patients with residual disease after PST. pCR remains a prognostic factor regardless of *gBRCA1/2m* status.⁸⁷⁻⁸⁹

In patients with stage II-III TNBC, a four-drug ChT regimen of taxane–carboplatin followed by AC or EC, all combined with pembrolizumab improved pCR rate and EFS at 3 years (hazard ratio 0.63, 95% CI 0.48-0.82, $P < 0.001$). Pembrolizumab was continued after surgery for nine 3-week cycles. The benefit from pembrolizumab was independent of PD-L1 status.⁹⁰ In a phase III trial using a nab-paclitaxel–anthracycline backbone, neoadjuvant atezolizumab also improved pCR rate regardless of PD-L1 status.⁹¹ A randomised phase II study using nab-paclitaxel and EC as ChT backbone with or without durvalumab (only given in the neoadjuvant setting) resulted in a numerical non-significant improvement in pCR rate but significantly improved EFS and OS.⁹²

Residual disease after neoadjuvant therapy. In the CREATE-X trial, adjuvant capecitabine improved DFS (hazard ratio 0.70, 95% CI 0.53-0.92, $P = 0.01$) and OS (hazard ratio 0.59, 95% CI 0.39-0.90, $P = 0.01$); this benefit was only significant in patients with TNBC tumours.⁹³ Two recent reviews found that adjuvant capecitabine improved OS, by a relative reduction of 12%-30% in patients with TNBC but little evidence of impact in those with HR-positive disease.^{94,95} Low-dose

capecitabine also improves outcomes after standard non-platinum-containing adjuvant ChT.⁹⁶

It is unknown whether post-neoadjuvant capecitabine adds benefit in patients receiving post-neoadjuvant continuation of their ICI or olaparib (indicated as adjuvant therapy for patients with *gBRCA1/2m* tumours and non-pCR or \geq pT2 or \geq pN1 if treated with initial surgery). No efficacy results are available for either of these combinations in the adjuvant setting. The understanding of safety of olaparib–capecitabine is also insufficient to support use of this combination.

Special situations.

Refer to the **Supplementary Material Section 8**, available at *Annals of Oncology* online, for further details on elderly patients, male breast cancer and other special populations.

Adjuvant therapy for DCIS

Surgery. Breast surgery for DCIS should follow the recommendations for invasive carcinoma, as discussed in the Locoregional Treatment – Surgery section of this document. For *in situ* disease, margins of ≥ 2 mm are preferred.⁶

ALN evaluation with SLNB is not routinely required in DCIS. To exclude microinvasive disease, SLNB should be considered if mastectomy is undertaken or for large (>5 cm) or high-risk DCIS. The likelihood of a positive SLN with pure DCIS is low (~5%).⁹⁷

RT. WBRT after BCS for DCIS halves the risk of local recurrence without impact on survival.⁹⁸ Total mastectomy with clear margins in DCIS is curative.⁹⁹ Young age, inadequate margins and greater disease volume are associated with higher risk of local recurrence after BCS with or without RT, while young age, high grade and microinvasion are associated with higher risk of local recurrence after mastectomy. In patients with low-risk DCIS (tumour size <10 mm, low or intermediate nuclear grade, adequate surgical margins), omitting RT can be an option.¹⁰⁰

Hypofractionated regimens can be used instead of longer treatment schedules; in intermediate/high-risk patients, the addition of a boost dose to the primary tumour

bed lowers recurrence rates.¹⁰¹ APBI is an alternative to WBRT for low-risk DCIS, as defined in the 'WBRT after BCS' subsection of this guideline.²⁹

Systemic therapy. In patients treated with BCT for HR-positive DCIS, both tamoxifen and AIs (postmenopausal patients only) reduce the risk of invasive and non-invasive recurrences and reduce the incidence of second primary (contralateral) breast cancer, albeit without an effect on OS.¹⁰²⁻¹⁰⁴ In the TAM-01 trial, low-dose tamoxifen (5 mg daily) also decreases the risk of recurrence after DCIS.¹⁰⁵

Recommendations

General treatment principles

- Where available, treatment should be carried out in specialised breast units/centres by a specialised MDT that can refer patients to other specialties [III, A].
- Participation in clinical trials is recommended [V, A].
- The treatment strategy for each patient should be based on an individual risk–benefit analysis considering the tumour burden (size and location of the primary tumour, number of lesions and extent of LN involvement) and biology (pathology, including biomarkers and gene expression), as well as age, menopausal status, general health status and patient preferences [I, A].
- Age should be considered in relation to other factors and should not be the primary determinant for treatment decisions [IV, A].
- Fertility and fertility preservation should be discussed with younger premenopausal patients (irrespective of stage of disease) before the initiation of any systemic treatment [V, A].¹⁰⁶

Patient communication and shared decision making

- Information on diagnosis and treatment choice should be given repeatedly (both verbally and in writing) in a comprehensive and easily understandable manner [V, A].
- The use of reliable, patient-centred websites or similar sources of information is recommended [V, A].

- Patients should be actively involved in all management decisions and should have equitable access to the full range of reproductive care options including pregnancy counselling, contraception and fertility preservation [V, A].

Locoregional treatment

- BCS with post-operative RT is the preferred local treatment option for the majority of patients with EBC [I, A].
- If mastectomy is indicated/preferred, breast reconstruction should be offered, except for primary inflammatory and other high-risk tumours where delays in systemic/radiation treatment would compromise care [V, A].
- SLNB is the standard axillary surgery in all cN0 patients [I, A].
- In the absence of prior PST, patients with micrometastatic spread and those with limited SLN involvement (1-2 affected SLNs) in cN0, following BCS with subsequent WBRT, eventually including the lower part of axilla and adjuvant systemic treatment, do not need further axillary surgery [II, A].
- ALND following positive SLNB with <3 involved SLNs is generally recommended only in case of expected high axillary disease burden or impact on further adjuvant systemic treatment decisions [II, A].
- Surgical planning following PST should consider the post-PST situation [II, A].
- WBRT is recommended after BCS [I, A].
- Hypofractionated schedules are recommended: moderate (i.e. 15-16 fractions of ≤ 3 Gy per fraction daily for all indications of post-operative RT) and ultra-hypofractionated [i.e. 26 Gy in five daily fractions for whole breast or chest wall (without reconstruction) irradiation] [I, A].
- APBI is an alternative treatment to WBRT in patients with invasive and *in situ* breast cancer at low local recurrence risk [I, A].
- PMRT is recommended for high-risk EBC, including involved resection margins, ≥ 4 involved ALNs, T3-T4 tumours and in the presence of combinations of other risk factors [I, A].
- PMRT should be considered in patients with intermediate-risk features (e.g. lymphovascular invasion, age), including those with 1-3 positive ALNs [I, A].

- Nodal RT is recommended for patients with involved LNs (the extent of target volumes depends on risk factors including the number of involved LNs, N-stage and response to PST) [I, B].
- If indicated, PMRT can be administered after immediate breast reconstruction [III, A].

HR-positive, HER2-negative EBC

- All luminal-like cancers should be treated with ET [I, A].
- Most luminal A-like tumours do not require ChT, except those with high disease burden [I, A].
- In cases of uncertainty about indications for adjuvant ChT (after consideration of all clinical and pathological factors), gene expression assays or endocrine response assessment can be used to guide decisions on adjuvant ChT [I, A].
- Luminal B-like HR-positive, HER2-negative tumours should be treated with ChT followed by ET. ChT should be considered in cases of high clinical risk (e.g. multinode-positive, premenopausal node-positive, locally advanced) and 0-3 involved LNs with high-risk features (e.g. high-risk gene expression assay result) [I, A].
- Premenopausal patients should receive either tamoxifen alone (luminal A like, stage I) [I, A], or in case of a high risk of recurrence, ovarian suppression with either OFS–tamoxifen [I, A] or OFS–AI [I, A].
- Postmenopausal patients should receive an AI or tamoxifen followed by an AI [I, A].
 - Tamoxifen can be given for lower-risk tumours or if AIs are not tolerated [I, A].
- Bisphosphonates (up to 5 years) are recommended in women without ovarian function (postmenopausal or undergoing OFS), especially if at high risk of relapse [I, A] or treatment-related bone loss [I, A].
- Abemaciclib for 2 years in addition to ET after completion of locoregional therapy should be considered in patients with stage III or high-risk stage II EBC [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: A].

- Extended ET beyond 5 years should be considered in high-risk EBC [I, A]; 7-8 years' treatment duration seems sufficient for most patients at high risk [I, A].
- Following completion of (neo)adjuvant and locoregional therapy, 1 year of adjuvant olaparib is recommended for patients with *gBRCA1/2m* and HER2-negative, HR-positive EBC with multiple positive LNs after primary surgery or residual high-risk EBC after neoadjuvant ChT [I, A; ESMO-MCBS v1.1 score: A; ESCAT: I-A].
- ET should be given concomitantly with adjuvant olaparib in *gBRCA1/2m* carriers [I, A].
- Olaparib and abemaciclib should not be combined due to overlapping toxicities but may be considered sequentially with olaparib first [V, A].

HER2-positive EBC

- HER2-directed therapy (with initial concurrent ChT) should be given for 12 months, covering both the neoadjuvant and/or adjuvant phases of treatment [I, A; ESCAT score I-A].
 - Administration can be combined—if indicated—with RT and ET [I, A]. In selected low-risk situations, 6 months of anti-HER2 therapy may be non-inferior.
 - Regular cardiac assessments are recommended (prior to, during and following therapy) with the option of additional assessments prior to the start of any ChT treatment [II, B].
- For patients with clinical stage II-III HER2-positive breast cancer (e.g. T >2 cm or node-positive), neoadjuvant systemic ChT with anti-HER2 therapy comprising trastuzumab–pertuzumab is the preferred option [I, A; ESCAT score I-A].
- For the ChT backbone, a regimen of anthracycline–taxane or taxane–carboplatin is evidence-based independent of neoadjuvant or adjuvant use [I, A].
- Dual blockade with HP (versus trastuzumab alone) combined with ChT achieves higher pCR rates and is recommended for neoadjuvant therapy [I, A; ESMO-MCBS v1.1 score: C; ESCAT score I-A].

- Patients with residual invasive disease (non-pCR after neoadjuvant ChT and anti-HER2 therapy) should receive adjuvant treatment with T-DM1 for up to 14 cycles [I, A; ESMO-MCBS v1.1 score: A; ESCAT score I-A].
- For patients with stage I (T1a-b N0) HER2-positive EBC, primary surgery may be carried out [III, B], followed by adjuvant administration of 12-weeks of paclitaxel plus 1 year of trastuzumab if clinical stage is confirmed by pathology [III, B; ESMO-MCBS v1.1 score: A; ESCAT score I-A].
- For patients with pathological stage II or III cancer treated with initial surgery, adjuvant ChT combined with 1 year of anti-HER2 therapy should be given [I, A; trastuzumab ESMO-MCBS v1.1 score: A; HP ESMO-MCBS v1.1 score: A; ESCAT score I-A].
- In patients with node-positive disease, the addition of pertuzumab to trastuzumab should be strongly considered in the adjuvant setting irrespective of HR status [I, A; ESMO-MCBS v1.1 score: A; ESCAT score I-A].
- Patients with high-risk HR-positive tumours may be considered for extended treatment with neratinib (concurrent with ET) for 1 year after completion of 1 year of trastuzumab or trastuzumab-based therapy [I, B; ESMO-MCBS v1.1 score: no evaluable benefit; ESCAT score I-A].

TNBC

- HER2-negative tumours with 1%-9% ER and/or PgR expression (ER-/PgR-low) are a heterogeneous group, some of which behave biologically similarly to TNBCs; therapeutic strategies should be adjusted to this specific situation since this might lead to a higher response to ChT and to reduced efficacy of ET compared with classical HR-positive breast cancer [II, B].
- TNBC tumours should be treated with ChT with or without an ICI (pembrolizumab) [I, A], except for some node-negative special histological subtypes such as secretory or adenoid cystic carcinomas or very low clinical risk (pT1a pN0) tumours [II, B].
- ChT should be administered for 12-24 weeks (4-8 cycles) depending on the stage of the disease, type of selected regimen and regardless of whether an ICI is added [I, A].

- The use of dose-dense schedules of ChT, with granulocyte colony-stimulating factor (G-CSF) support, should be considered given their documented benefit over non-dose-dense schedules [I, A].
- For cT1c-4 N0, or any N-positive TNBC, neoadjuvant treatment is preferred [I, A].
- cT2-4 N0 or any N-positive (stage II-III) TNBC should be treated with neoadjuvant ChT plus pembrolizumab unless there are risk factors for excessive ICI-associated immune toxicity [I, A; ESMO-MCBS v1.1 score: A].
- Pembrolizumab should be administered every 3 weeks throughout the neoadjuvant phase [I, A] and for nine 3-week cycles during the adjuvant phase, regardless of pCR status [I, A; ESMO-MCBS v1.1 score: A].
- Patients receiving pembrolizumab should be monitored very closely for the risk of immune-related adverse events throughout treatment and following the ESMO CPG for the management of toxicities from immunotherapy [V, A].¹⁰⁷
- An ICI should not be given solely as adjuvant therapy without prior neoadjuvant ICI treatment [V, D].
- In patients with *gBRCA1/2m* and high-risk TNBC (non-pCR or pathological stage II-III), 1 year of adjuvant olaparib should be administered [I, A; ESMO-MCBS v1.1 score: A; ESCAT: I-A].
 - The combination of ICIs and olaparib may be considered on an individual basis [V, C].
- Patients with residual disease who did not receive ICIs should be offered adjuvant capecitabine for 6-8 cycles [I, A].
 - The combination of olaparib and capecitabine in patients with *gBRCAm* should not be used [I, E].
 - The combination of ICI and capecitabine may be considered on an individual basis [V, C].

Special situations

- Treatment of elderly patients should be adapted to biological (not chronological) age, with consideration of less aggressive regimens in frail patients. In patients suitable for standard ChT, a standard multidrug regimen should be used [II, B].

- A geriatric assessment should be carried out before making treatment decisions [II, A].
- Tamoxifen is the standard adjuvant ET for male patients with breast cancer [IV, A].
- As with premenopausal women with breast cancer, a gonadotropin-releasing hormone agonist (GnRHa) may be added in higher-risk male patients with breast cancer, and a combination of AI-GnRHa should be considered in cases where tamoxifen is contraindicated [IV, B].
- An AI must be administered with a GnRHa when used as adjuvant ET in male patients with breast cancer [IV, A].
- In male patients with breast cancer, ChT, ET, anti-HER2, ICI, CDK4/6 inhibitor and PARP inhibitor therapy indications and regimens should follow the same recommendations as those for breast cancer in female patients [IV, A].
- DCIS should be preferentially treated with BCS and WBRT or, in cases of extensive or multicentric DCIS, mastectomy [I, A].
- Both tamoxifen and AIs may be used after local BCT for DCIS to prevent local recurrence and to decrease the risk of developing a second primary breast cancer [I, B].
- Following mastectomy for DCIS, tamoxifen or AIs might be considered to decrease the risk of contralateral breast cancer in patients with a high risk of new breast tumours [II, B].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

General follow-up considerations

The aims of follow-up are:

- To detect local and/or regional recurrences or contralateral breast cancers that are potentially curable
- To evaluate and treat therapy-related side-effects and complications
- To promote adherence to adjuvant systemic treatment
- To provide support to enable a return to normal life after breast cancer
- To detect second primary cancers

Even though no data exist from recent randomised trials involving modern imaging to support any particular follow-up sequence or protocol, surveillance should balance patient needs, follow-up costs and burden on the health care system. The follow-up strategy should consider differential recurrence patterns as determined by tumour biology.

Reproductive and sexual health considerations

The number of survivors following treatment for an initial presentation is increasing. Therefore, long-term consequences related to the different treatment modalities must be recognised and followed (**Supplementary Table S6**, available at *Annals of Oncology* online).

Premature menopause and infertility represent extremely important potential consequences of EBC treatment, particularly affecting premenopausal women and with significant impact on quality of life (QoL). Side-effects of ET and sexual dysfunction affect women of all ages and should be addressed to improve QoL and ensure treatment adherence. Although a few patients experience temporary amenorrhoea, a subset will experience treatment-related permanent ovarian dysfunction, with risk increasing with age.¹⁰⁸ Even in patients that recover ovarian function, premature menopause and infertility represent significant concerns. Addressing these possibilities before therapy, and involving a fertility specialist to consider preservation strategies, is indicated in all premenopausal women considering a future pregnancy. Available data suggest that pregnancy is safe after breast cancer treatment.¹⁰⁹

Psychosocial considerations

Long-term survivorship issues need particular attention and involve all the implications of living after a breast cancer diagnosis. Patients should be encouraged to adopt a healthy lifestyle, exercise regularly and avoid being overweight.

Psychological and other practical consequences of the disease and its treatment are an extremely important part of long-term care. Patients should be followed and managed for issues such as anxiety, depression, uncertainty about the future, sleep disturbances, sexuality, chronic fatigue, neurocognitive dysfunction and direct or indirect consequences on their ability to work and care for their families. While

addressing long-term care and follow-up, the broader dimensions of culture and context that impact implementation of follow-up strategies should be considered. Long-term survivorship considerations should include all psychosocial needs of patients once treatment ends.

Ultimately, these issues have a significant influence on the QoL of individual patients and deserve the organisation of a diagnostic, educational and management infrastructure with adequate human resources and a close multidisciplinary follow-up.

Recommendations

General follow-up considerations

- Regular follow-up visits are recommended every 3 months in the first 3 years post-treatment (every 6 months for low-risk EBC), every 6 months from years 4-5 and annually thereafter. The interval of visits can be adapted to the risk of relapse and patient needs [V, A].
- Annual bilateral (after BCT) or contralateral mammography (after mastectomy) is recommended, plus US and breast MRI, when needed [II, A].
- Breast cancer survivors should participate in national screening programmes for other cancers [V, B].
- In asymptomatic patients, laboratory tests (e.g. blood counts, routine chemistry, tumour marker assessment) or other imaging are not recommended [I, D].¹¹⁰
- Symptom-directed investigations should be considered as indicated [V, B].
- Regular bone density evaluation is recommended for patients on AIs or undergoing OFS [I, A].
- In asymptomatic patients with normal cardiac function who have received potentially cardiotoxic treatment, cardiac follow-up should be carried out as clinically indicated [III, B].^{111,112}
- For patients on tamoxifen, an annual gynaecological examination is recommended [V, B]; however, routine transvaginal US is not recommended [V, D].²

Reproductive and sexual considerations

- Premature menopause, infertility and potential sexual dysfunction should be discussed and addressed with each patient, when appropriate, before the start of adjuvant therapy [V, A].
- Premenopausal women considering pregnancy should be informed that available evidence suggests that pregnancy seems to be safe after breast cancer treatment [III, A].
- For women desirous of pregnancy, temporary interruption of adjuvant ET after 18-30 months of ET, allowing a wash-out period of 3 months, and attempting to get pregnant during a period of up to 2 years, followed by resumption of ET, does not appear to impact short-term breast cancer outcomes in lower-risk HR-positive, HER2-negative EBC [III, A].¹¹³

Psychosocial considerations

- Patients should be encouraged to adopt a healthy lifestyle, exercise regularly, avoid being overweight and minimise alcohol intake [II, A].
- Long-term survivorship considerations, including psychological needs and issues related to work, family and sexuality, should be addressed [V, A].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development (<https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>). The relevant literature has been selected by the expert authors. A table of ESCAT scores is included in **Supplementary Table S7**, available at *Annals of Oncology* online. ESCAT scores have been defined by F. André and G. Curigliano on behalf of the authors and assisted, as needed, by the ESMO Translational Research and Precision Medicine Working Group.¹¹⁴ A table of ESMO-MCBS scores is included in **Supplementary Table S8**, available at *Annals of Oncology* online. ESMO-MCBS v1.1¹¹⁵ was used to calculate scores for therapies/indications approved by the EMA or FDA (<https://www.esmo.org/Guidelines/ESMO-MCBS>). The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is

reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in **Supplementary Table S9**, available at *Annals of Oncology* online.¹¹⁶ Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website (<https://www.esmo.org/guidelines/guidelines-by-topic/breast-cancer/early-breast-cancer>).

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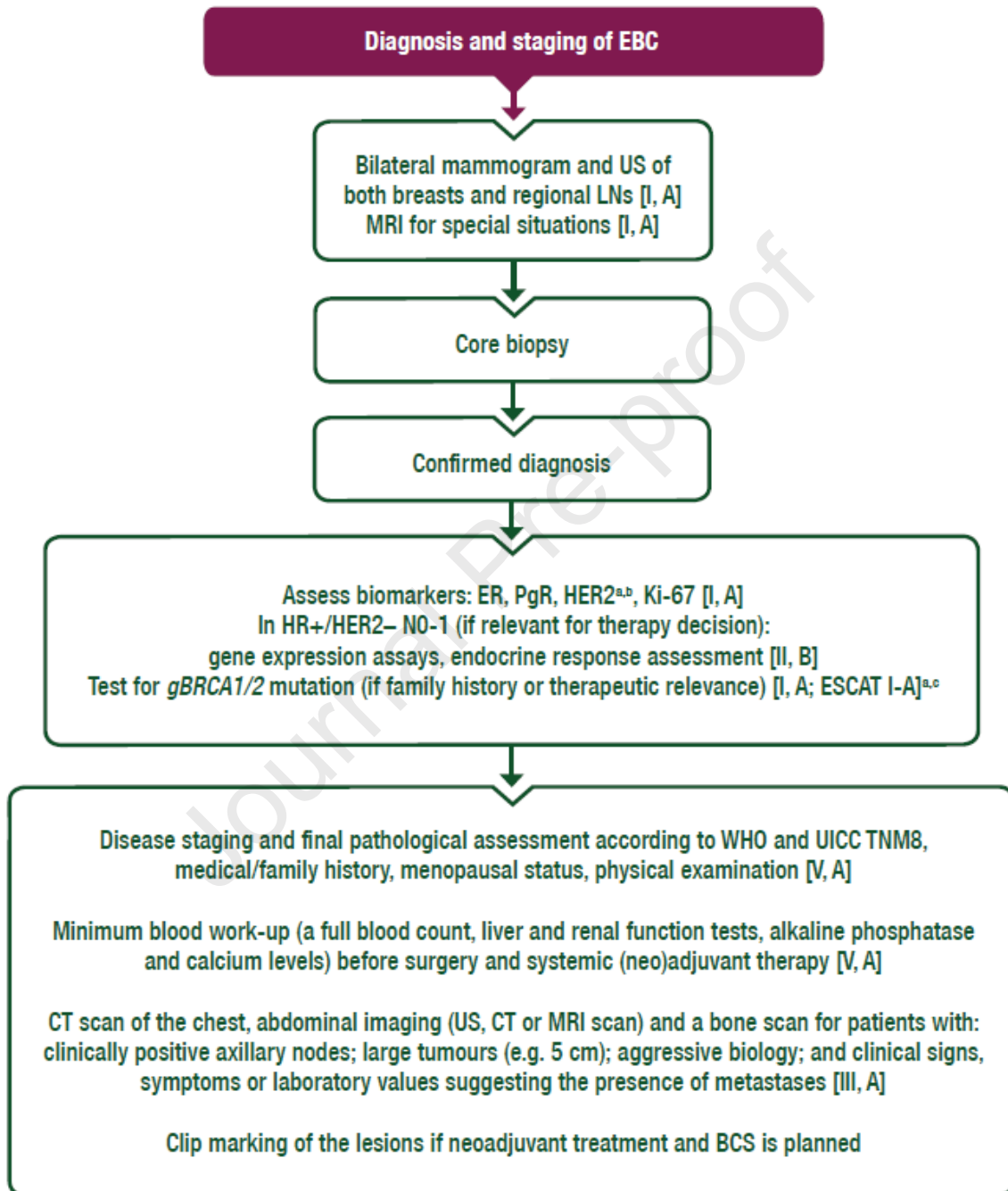
BX reports personal fees for advisory board membership from AstraZeneca and Novartis; personal fees as an invited speaker from Pfizer and Roche; and an institutional research grant from Henrui (non-financial interest).

GC reports personal fees for advisory board membership from AstraZeneca, BMS, Celcuity, Daiichi Sankyo, Ellipsis, Exact Sciences, Lilly, Merck, Pfizer, Roche and Veracyte; personal fees as an invited speaker from AstraZeneca, Daiichi Sankyo, Novartis, Pfizer and Roche; personal fees for a writing engagement from Pfizer; an institutional research grant from Merck for an investigator-initiated trial; institutional funding for Phase I studies from Astellas, AstraZeneca, Blueprint Medicine, BMS, Daiichi Sankyo, Kymab, Novartis, Philogen, Relay Therapeutics (coordinating PI), Roche and Sanofi; non-remunerated roles as Advisor for the Ministry of Health at the Italian National Health Council; as Chair of the ESMO Clinical Practice Guidelines Committee; as a member of the scientific council at Europa Donna, of the advisory council for EUSOMA and of the Board of Directors at Lega Italiana Lotta ai Tumori; and a non-remunerated advisory role at Fondazione Beretta.

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FIGURES

Figure 1. Diagnostic work-up and staging of EBC



Purple: general categories or stratification; white: other aspects of management.

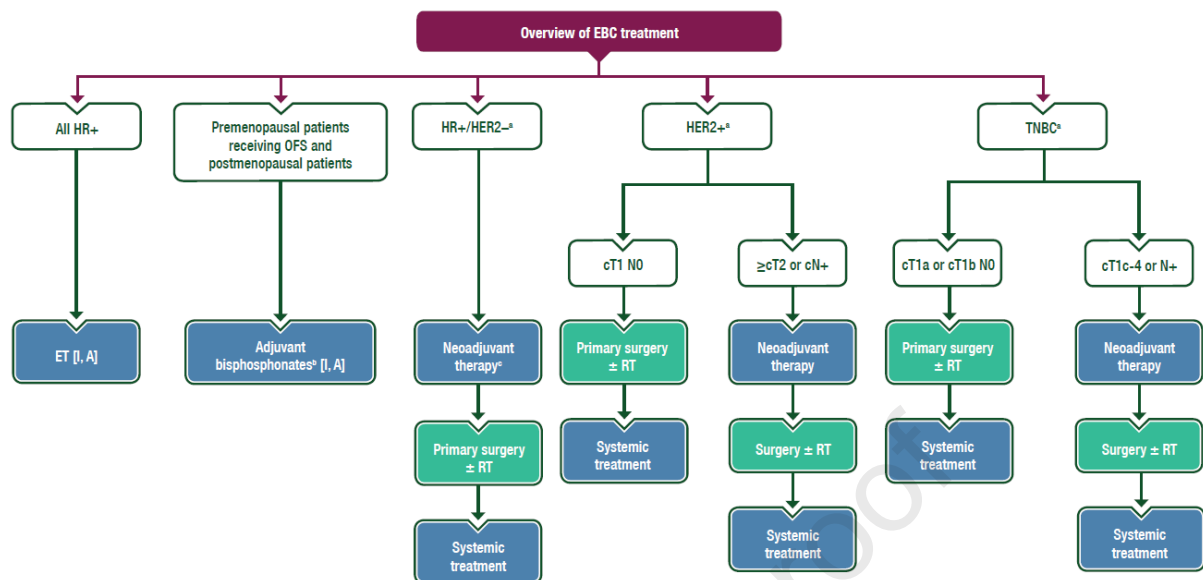
BCS, breast-conserving surgery; CISH, chromogenic *in situ* hybridisation; CPG, Clinical Practice Guideline; CT, computed tomography; EBC, early breast cancer;

ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; *gBRCA1/2*; germline *BRCA1/2*; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LN, lymph node; MRI, magnetic resonance imaging; N, node; PgR, progesterone receptor; TNM8, tumour–node–metastasis eighth edition; UICC, Union for International Cancer Control; US, ultrasound; WHO, World Health Organization.

^aESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and assisted as needed by the ESMO Translational Research and Precision Medicine Working Group.¹¹⁴ See **Supplementary Table S7**, available at *Annals of Oncology* online, for more information on ESCAT scores.

^bESCAT score only applicable if HER2 gene amplification assessed by FISH/CISH.

^cDetailed rationale for *gBRCA1/2* mutation testing is covered in the ESMO CPG for risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes.⁴

Figure 2. EBC treatment overview

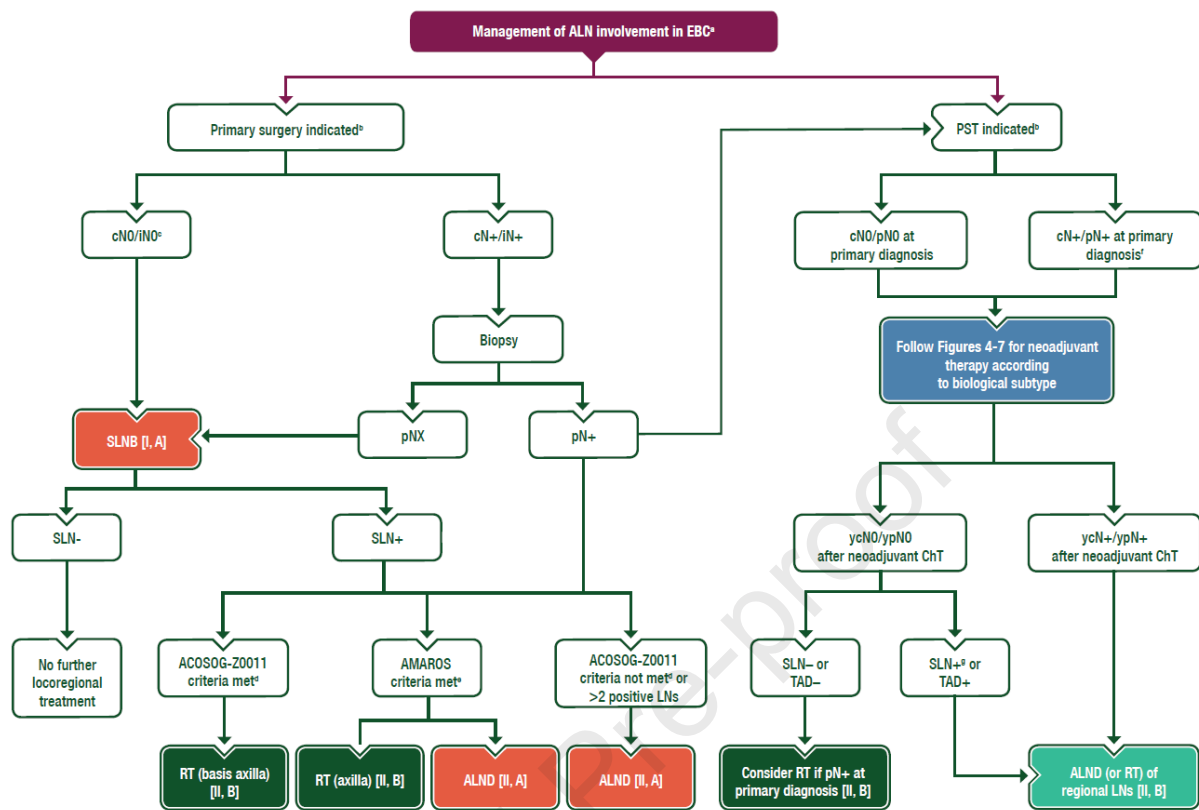
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy.

ALN, axillary lymph node; c, clinical; ChT, chemotherapy; CPG, Clinical Practice Guideline; DCIS, ductal carcinoma *in situ*; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; N, node; OFS, ovarian function suppression; T, tumour; TNBC, triple-negative breast cancer; RT, radiotherapy.

^aSee **Figure 3** for management of ALN involvement and **Figures 4-7** for systemic therapy according to breast cancer subtype. Recommendations for special situations (elderly patients, male breast cancer and DCIS) are described in the CPG text.

^bBisphosphonates are approved for treating bone metastases and osteoporosis and not for prevention of relapse.

^cIf ChT is indicated it may be given in the neoadjuvant setting.

Figure 3. Management of ALN involvement in EBC

Purple: general categories or stratification; red: surgery; turquoise: combination of treatments or other systemic treatments; blue: systemic anticancer therapy; dark green: RT; white: other aspects of management.

ALN, axillary lymph node; ALND, axillary lymph node dissection; c, clinical; ChT, chemotherapy; CT, computed tomography; EBC, early breast cancer; i, imaging; ITC, isolated tumour cell; LN, lymph node; MDT, multidisciplinary team; MRI, magnetic resonance imaging; N, node; p, pathological; PET, positron emission tomography; PST, primary systemic therapy; RT, radiotherapy; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection; US, ultrasound.

^aDiscuss in MDT whether number of LNs is important for systemic therapy allocation.

^bSee **Figure 2** for an overview of primary surgery and neoadjuvant therapy indications.

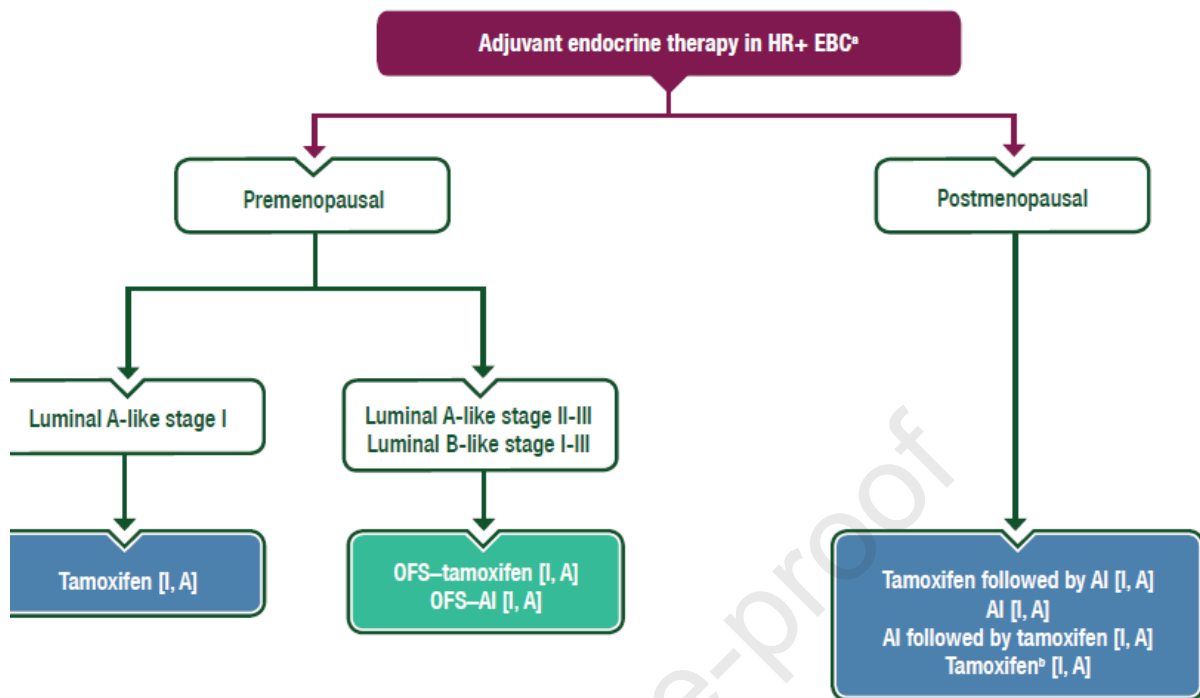
^cImaging (axillary US is preferred but MRI and PET-CT may be used in specific cases where more detailed imaging is required).

^dRefers to ACOSOG-Z0011 trial eligibility criteria.¹²

^eRefers to AMAROS trial eligibility criteria.¹¹⁷ OTOASOR trial criteria can also be considered.¹⁷

^fInflammatory breast cancer and patients with N2 or N3 stage disease should receive ALND unless otherwise defined in a clinical trial.

^gIf ITCs are detected, consider axillary and locoregional RT as an alternative to ALND if an impact on adjuvant systemic treatments is not anticipated.

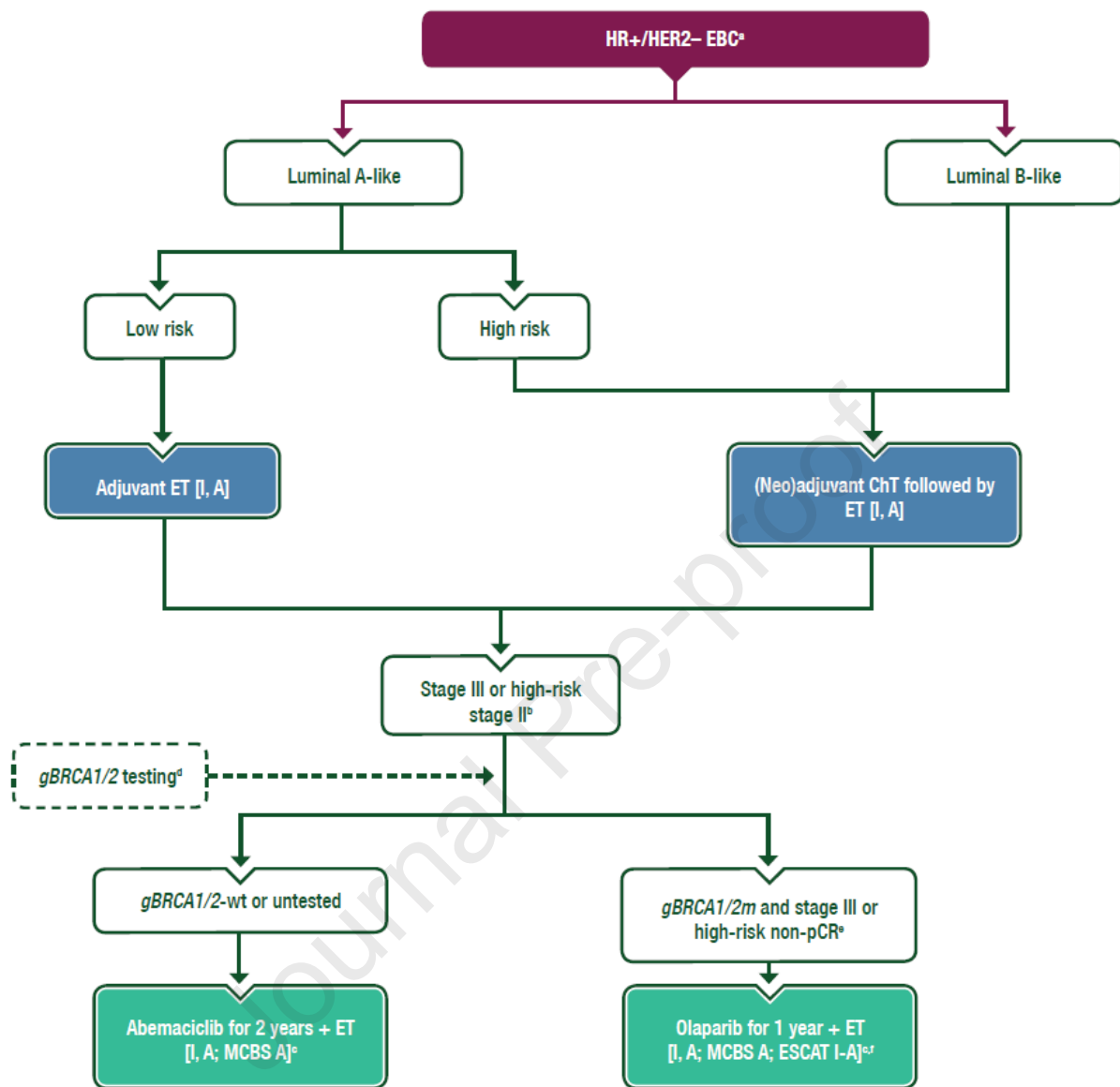
Figure 4. Role of adjuvant endocrine therapy in HR-positive EBC

Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy.

AI, aromatase inhibitor; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OFS, ovarian function suppression.

^aSee **Figure 2** for the role of surgery in HR-positive, HER2-negative EBC.

^bTamoxifen can be given for lower-risk tumours or if AIs are not tolerated [I, A].

Figure 5. Systemic treatment of HR-positive, HER2-negative EBC

Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy.

ChT, chemotherapy; CPS+EG, pretreatment clinical stage and post-treatment pathological stage, estrogen receptor and tumour grade; EBC, early breast cancer; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ET, endocrine therapy; FDA, Food and Drug Administration; *gBRCA1/2*; germline *BRCA1/2*; HER2, human epidermal growth factor receptor 2;

HR, hormone receptor; m, mutation; MCBS, ESMO-Magnitude of Clinical Benefit Scale; N, node; pCR, pathological complete response; wt, wild type.

^aSee **Figure 2** for the role of surgery in HR-positive, HER2-negative EBC.

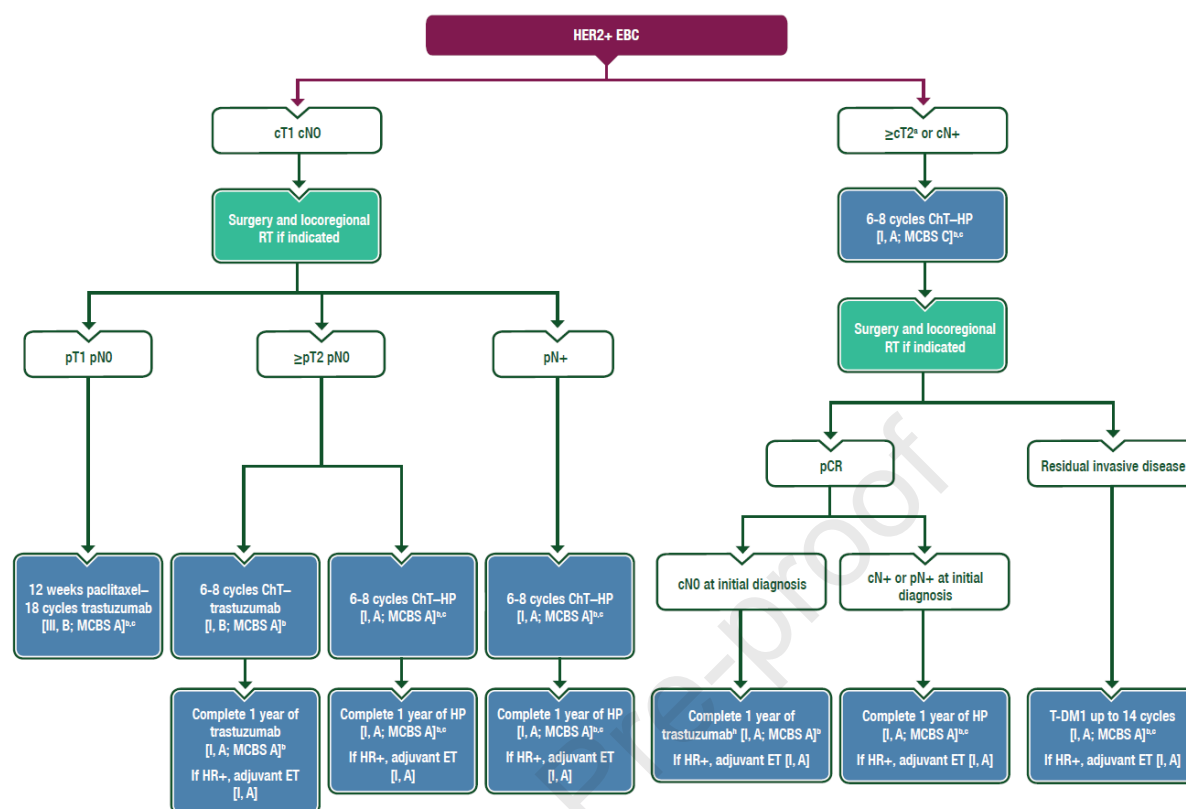
^bStage N1 with primary tumour >5 cm, and/or grade 3 and/or Ki-67 ≥20%.

^cESMO-MCBS v1.1¹¹⁵ was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>).

^dIf *gBRCA1/2* testing is appropriate and feasible.

^ePatients with HR-positive tumours and non-pCR after neoadjuvant ChT require a CPS+EG score ≥3 to receive olaparib.¹¹⁸

^fESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and assisted as needed by the ESMO Translational Research and Precision Medicine Working Group.¹¹⁴ See **Supplementary Table S7**, available at *Annals of Oncology* online, for more information on ESCAT scores.

Figure 6. Management of HER2-positive EBC

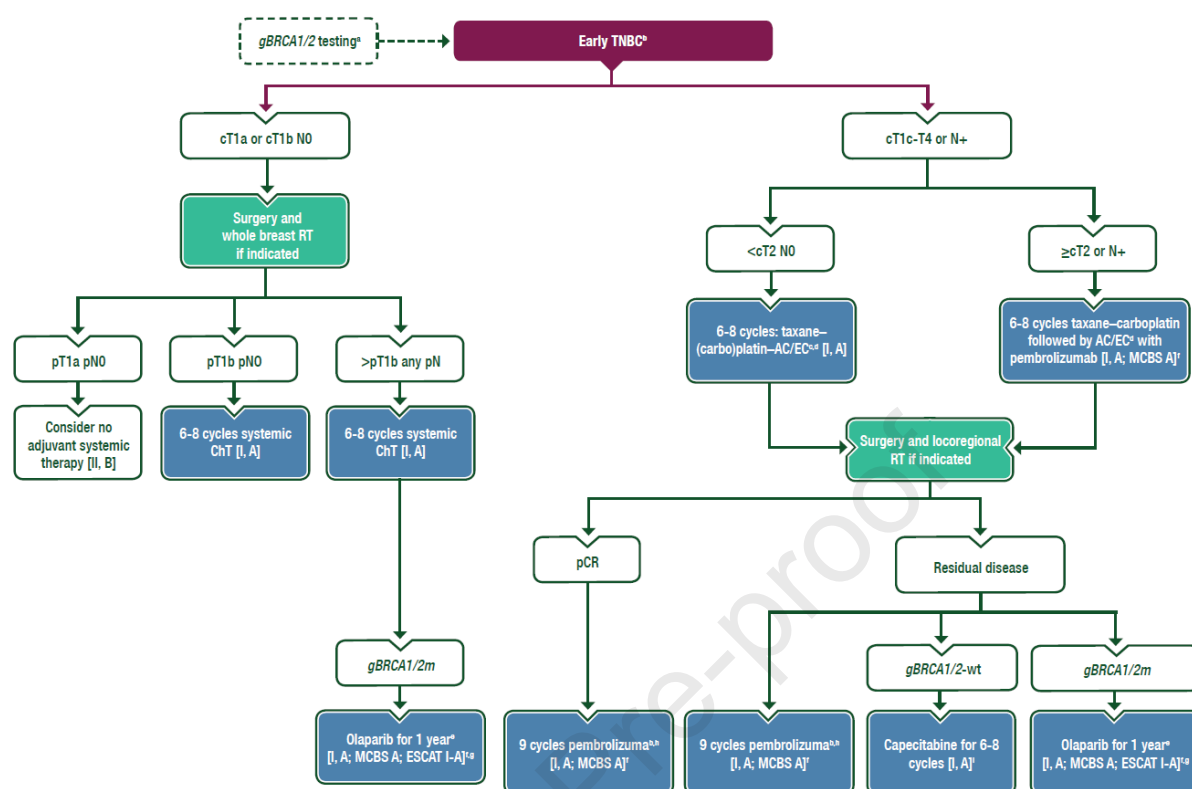
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy; dashed line: optional recommendation.

c, clinical; CISH, chromogenic *in situ* hybridisation; ChT, chemotherapy; EBC, early breast cancer; EMA, European Medicines Agency; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HP, trastuzumab–pertuzumab; HR, hormone receptor; MCBS, ESMO-Magnitude of Clinical Benefit Scale; N, node; p, pathological; pCR, pathological complete response; RT, radiotherapy; T, tumour; T-DM1, trastuzumab emtansine.

^aTumours <2 cm can be considered for neoadjuvant therapy.

^bESMO-MCBS v1.1¹¹⁵ was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>).

°ESCAT score I-A if HER2 gene amplification by FISH/CISH. ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and assisted as needed by the ESMO Translational Research and Precision Medicine Working Group.¹¹⁴ See **Supplementary Table S7**, available at Annals of Oncology online, for more information on ESCAT scores.

Figure 7. Management of early TNBC

Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.; blue: systemic anticancer therapy; dashed line: optional recommendation.

AC, doxorubicin–cyclophosphamide; c, clinical; ChT, chemotherapy; CPG, Clinical Practice Guideline; EC, epirubicin–cyclophosphamide; EMA, European Medicines Agency; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ER; estrogen receptor; ET, endocrine therapy; FDA, Food and Drug Administration; *gBRCA1/2*, germline *BRCA1/2*; G-CSF, granulocyte colony-stimulating factor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICI, Immune checkpoint inhibitor; m, mutation; MCBS, ESMO-Magnitude of Clinical Benefit Scale; N, node; p, pathological; pCR, pathological complete response; PgR, progesterone receptor; RT, radiotherapy; T, tumour; TNBC, triple-negative breast cancer; wt, wild type.

^aSee the ESMO CPG for risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes.⁴

^bHER2– tumours with 1%-9% ER and/or PgR expression (ER-low/PgR-low) are a heterogenous group, some of which behave biologically similarly to TNBC; therapeutic strategies should be adjusted to this specific situation since this might lead to a higher response to ChT and to reduced efficacy of ET compared with classical HR+ breast cancer [II, B].

^cThese evidence-based regimens without ICIs are sequential: anthracycline-based therapy followed by a taxane or taxane–carboplatin or vice versa.

^dThe use of dose-dense schedules of ChT, with G-CSF support, should be considered given their documented benefit over non-dose-dense schedules [I, A].

^eIndicated as adjuvant therapy for patients with *gBRCA1/2m* tumours and non-pCR or \geq pT2 or \geq pN1 if treated with initial surgery.

^fESMO-MCBS v1.1¹¹⁵ was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>).

^gESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and assisted as needed by the ESMO Translational Research and Precision Medicine Working Group.¹¹⁴ See **Supplementary Table S7**, available at *Annals of Oncology* online, for more information on ESCAT scores.

^hOnly if pembrolizumab was given preoperatively.

ⁱOnly for ICI-naïve patients.

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Diagnosis and staging of EBC

Bilateral mammogram and US of both breasts and regional LNs [I, A]
MRI for special situations [I, A]

Core biopsy

Confirmed diagnosis

Assess biomarkers: ER, PgR, HER2^{a,b}, Ki-67 [I, A]
In HR+/HER2- NO-1 (if relevant for therapy decision):
gene expression assays, endocrine response assessment [II, B]
Test for *gBRCA1/2* mutation (if family history or therapeutic relevance) [I, A; ESCAT I-A]^{a,c}

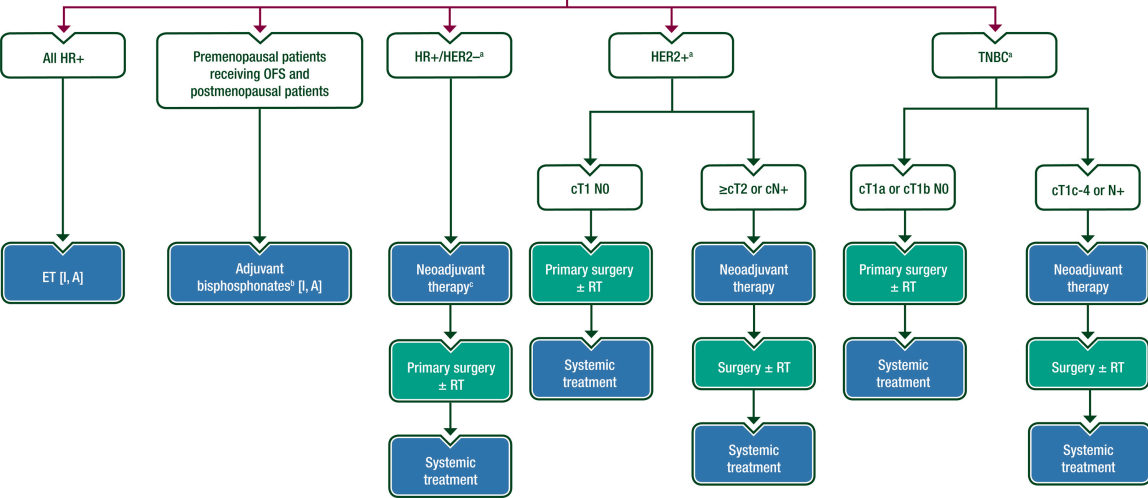
Disease staging and final pathological assessment according to WHO and UICC TNM8,
medical/family history, menopausal status, physical examination [V, A]

Minimum blood work-up (a full blood count, liver and renal function tests, alkaline phosphatase and calcium levels) before surgery and systemic (neo)adjuvant therapy [V, A]

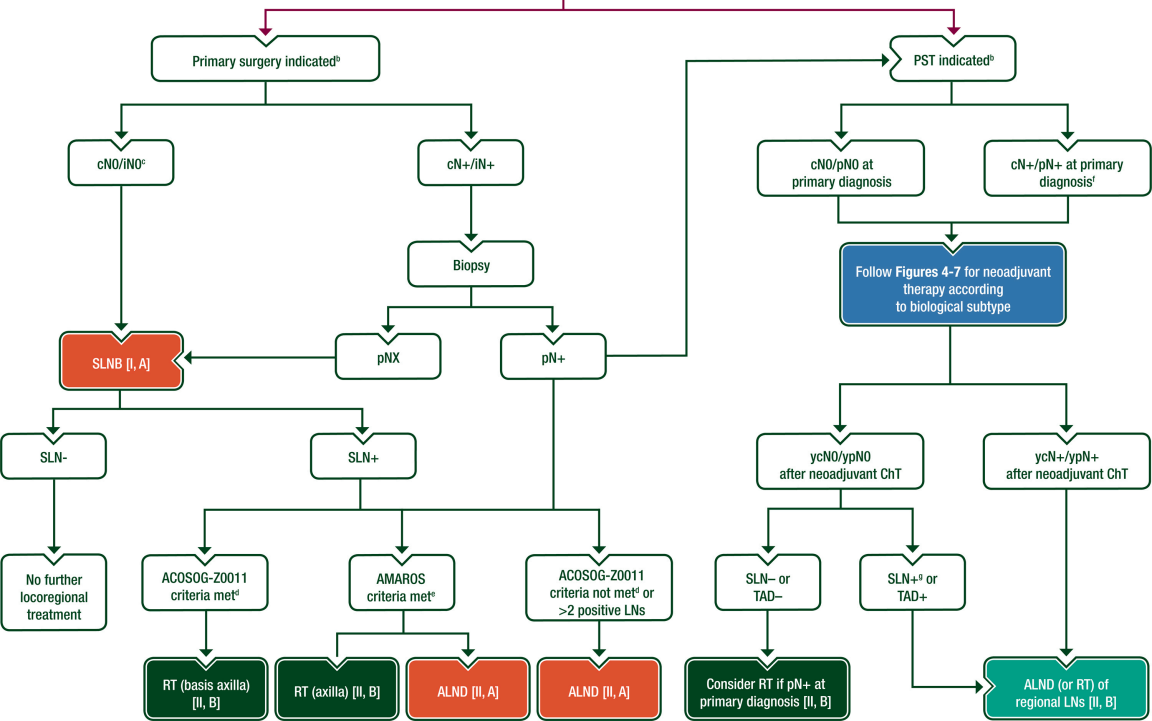
CT scan of the chest, abdominal imaging (US, CT or MRI scan) and a bone scan for patients with:
clinically positive axillary nodes; large tumours (e.g. 5 cm); aggressive biology; and clinical signs, symptoms or laboratory values suggesting the presence of metastases [III, A]

Clip marking of the lesions if neoadjuvant treatment and BCS is planned

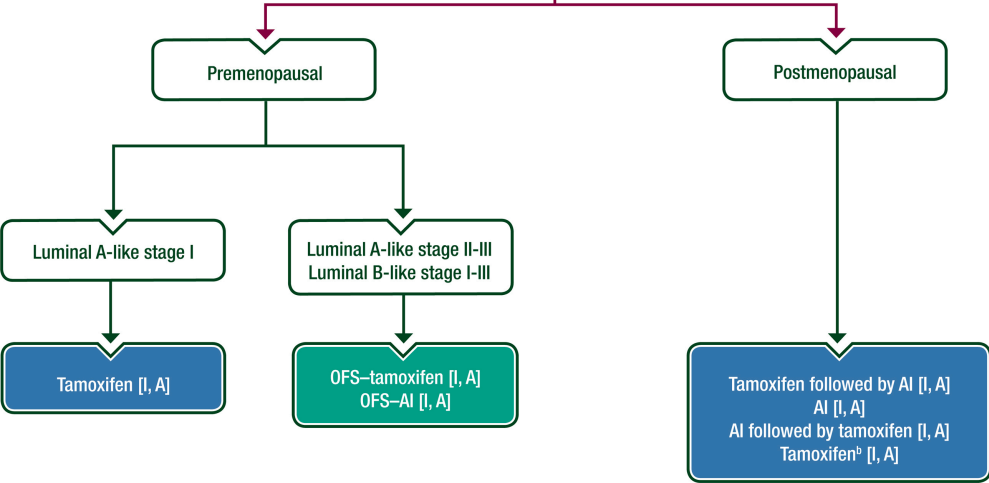
Overview of EBC treatment



Management of ALN involvement in EBC^a



Adjuvant endocrine therapy in HR+ EBC^a



HR+/HER2- EBC^a

Luminal A-like

Luminal B-like

Low risk

High risk

Adjuvant ET [I, A]

(Neo)adjuvant ChT followed by
ET [I, A]

Stage III or high-risk
stage II^b

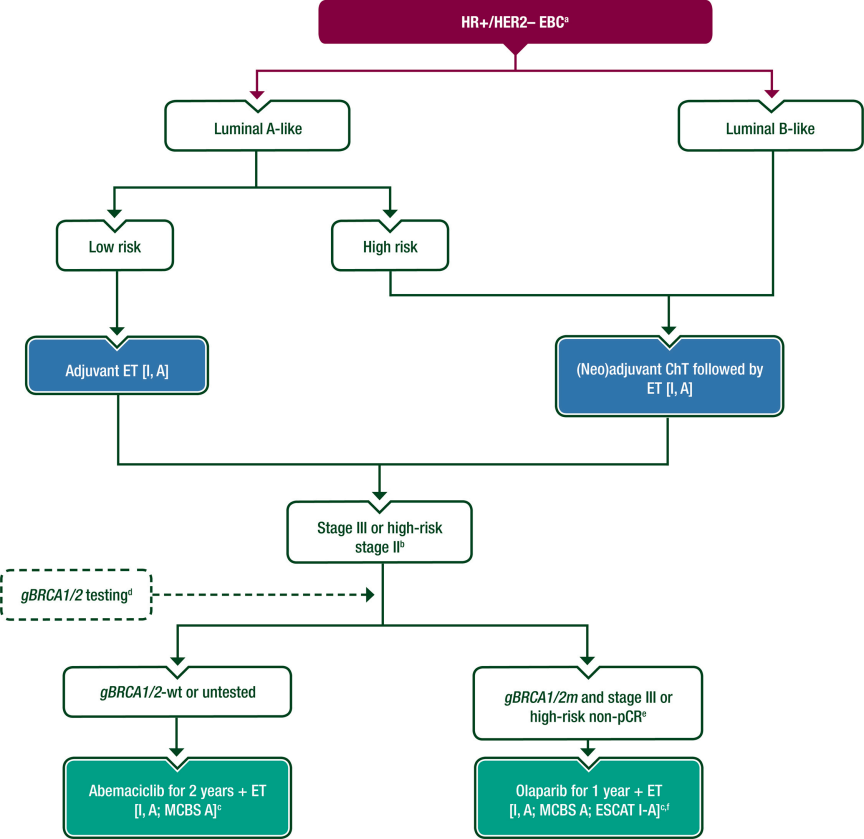
gBRCA1/2 testing^d

gBRCA1/2-wt or untested

Abemaciclib for 2 years + ET
[I, A; MCBS A]^e

*gBRCA1/2*m and stage III or
high-risk non-pCR^e

Olaparib for 1 year + ET
[I, A; MCBS A; ESCAT I-A]^{c,f}



HER2+ EBC

