National Breast Cancer

Clinical practice guideline

2025

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Adapted from NCCN, ESMO, and St Gallen Guidelines, incorporating local expert consensus and Maldivian healthcare context.

1. Introduction

Breast cancer is the most frequently diagnosed malignancy among women in the Maldives and remains a leading cause of cancer-related mortality. Over the past decade, the number of newly diagnosed cases has steadily increased, reflecting both improved detection and the country's ongoing demographic and lifestyle transitions. In the Maldivian context, late presentation and limited access to advanced diagnostic and treatment facilities continue to be major challenges, particularly for patients residing in atolls distant from Malé.

The formulation of national breast cancer clinical practice guidelines is therefore a crucial step toward standardizing and improving the quality of cancer care across all levels of the Maldivian health system. These guidelines aim to provide clinicians with clear, evidence-based recommendations for the prevention, early detection, diagnosis, treatment, and follow-up of breast cancer, while taking into account the unique healthcare realities and resource limitations of the Maldives.

This document integrates authoritative international standards, principally the **National Comprehensive Cancer Network (NCCN)**, the **European Society for Medical Oncology (ESMO)**, and the **St Gallen International Consensus** and adapts them through consultation with local oncology experts, surgeons, radiologists, pathologists, and public health stakeholders. The adaptation ensures that recommendations are both scientifically rigorous and feasible for implementation within the existing Maldivian infrastructure.

By unifying the management of early and metastatic breast cancer into one comprehensive reference, the guideline also supports coordinated care pathways, multidisciplinary team decision-making, and equitable patient access to essential services such as radiotherapy, systemic therapy, pathology, and imaging. Ultimately, the goal is to improve survival, quality of life, and patient experience, while guiding national policy and resource allocation for cancer control and prevention in the Maldives.

2. Literature Review

The development of this national guideline was informed by an extensive review of international and regional evidence-based standards for breast cancer management. The objective of this review was to identify high-quality, authoritative clinical practice guidelines and research data that could be appropriately adapted to the Maldivian healthcare context while ensuring scientific rigor and feasibility of implementation.

Globally, the **National Comprehensive Cancer Network (NCCN)** and the **European Society for Medical Oncology (ESMO)** remain the most widely recognized authorities in oncology guideline development. The NCCN Guidelines for Breast Cancer (Version 2025) provide a detailed, evidence-graded framework for screening, diagnosis, staging, treatment, and surveillance across all disease stages. ESMO Guidelines, last updated in 2024, emphasize multidisciplinary coordination, personalized medicine, and integration of molecular profiling in therapeutic decision-making. Both sets of guidelines are strongly supported by large-scale phase III clinical trials and meta-analyses that shape modern breast cancer management worldwide.

Complementary to these, the **St Gallen International Breast Cancer Consensus Conference (2023)** provides valuable expert-derived recommendations on classification of intrinsic subtypes (Luminal A, Luminal B, HER2-enriched, and triple-negative), the role of genomic signatures, and treatment stratification based on biological markers. These insights have been instrumental in the evolution of precision oncology, allowing clinicians to move beyond traditional histopathological criteria to individualized treatment approaches.

Regional adaptations were also reviewed from the **UK NICE guidelines**, **ASCO (American Society of Clinical Oncology)** statements, and selected Asian and small-island frameworks including those from **Singapore**, **Sri Lanka**, and **Mauritius**, whose healthcare structures and population sizes are comparable to the Maldives. Such regional comparisons provided practical insights into the integration of evidence-based protocols in resource-limited or geographically dispersed settings, highlighting strategies for equitable access to diagnostics, systemic therapy, and radiotherapy services.

In addition to guideline reviews, relevant epidemiological data were drawn from **Globocan 2024**, the **World Health Organization**, and the **Maldives National Cancer Registry (Ministry of Health, 2024)**. According to these sources, breast cancer constitutes nearly one-third of all cancers diagnosed in Maldivian women, with a rising incidence over the past decade. Most patients continue to present at stage II or higher, underscoring the need for robust screening and early detection strategies.

Emerging international evidence was also considered in the context of evolving treatment paradigms. Recent advances in endocrine therapy, CDK4/6 inhibitors, HER2-directed therapies (trastuzumab deruxtecan, pertuzumab, tucatinib), and immunotherapy for triple-negative breast cancer (pembrolizumab, atezolizumab) have dramatically changed outcomes for metastatic disease. Equally, in early-stage disease, shorter hypo fractionated radiotherapy schedules, genomic recurrence scores,

and extended adjuvant endocrine therapy have refined treatment personalization while maintaining cost-effectiveness.

This guideline therefore synthesizes international best practice with pragmatic adaptation to the Maldivian setting taking into account available surgical expertise, pathology capabilities, radiotherapy access, chemotherapy capacity, and the Aasandha-funded referral pathways for advanced diagnostics such as PET-CT.

In summary, the literature review establishes a solid scientific foundation for these national guidelines. It ensures that every recommendation aligns with the highest global standards of care while remaining adaptable, sustainable, and relevant to the evolving oncology landscape of the Maldives.

3. Case Definitions

Early Breast Cancer: Tumours confined to the breast and axillary nodes without distant metastasis.
Locally Advanced Breast Cancer: Tumours extending to chest wall or skin but without distant metastasis.
Metastatic Breast Cancer (MBC): Presence of distant organ metastasis confirmed radiologically or pathologically.
Subtypes are defined by receptor status (ER, PgR, HER2) and Ki67 proliferation index.

Triple Negative Breast Cancer (TNBC): Defined by the absence of expression of ER and PgR receptors and of overexpression of HER2 or amplification of *HER2neu*.

ChT: Chemotherapy

NCCN: National Cancer Network

ESMO: European Society of Medical Oncology

AJCC Classification: American Joint Committee on Cancer

RT: Radiotherapy

ET: Endrocrine therapy

BCS: Breast Conservation Surgery

SLNB: Sentinel lymph node biopsy

ALND: Axillary lymph node dissection

WBRT: Whole body radiotherapy

PST: Primary systemic treatment

PMRT: Post mastectomy radiotherapy

DCIS: Ductal Carcinoma In situ

4. Methodology

The development of this guideline was based on:

• Review of the latest NCCN and ESMO breast cancer guidelines.

• Consensus from Maldivian specialists across IGMH, Tree Top Hospital, and ADK Hospital across relevant specialties.

• Consideration of local resources, including diagnostic, surgical, and systemic therapy capacities.

• Adaptation to the Maldivian referral framework and Aasandha-funded treatment pathways.

5. Signs and Symptoms

Common presenting symptoms include

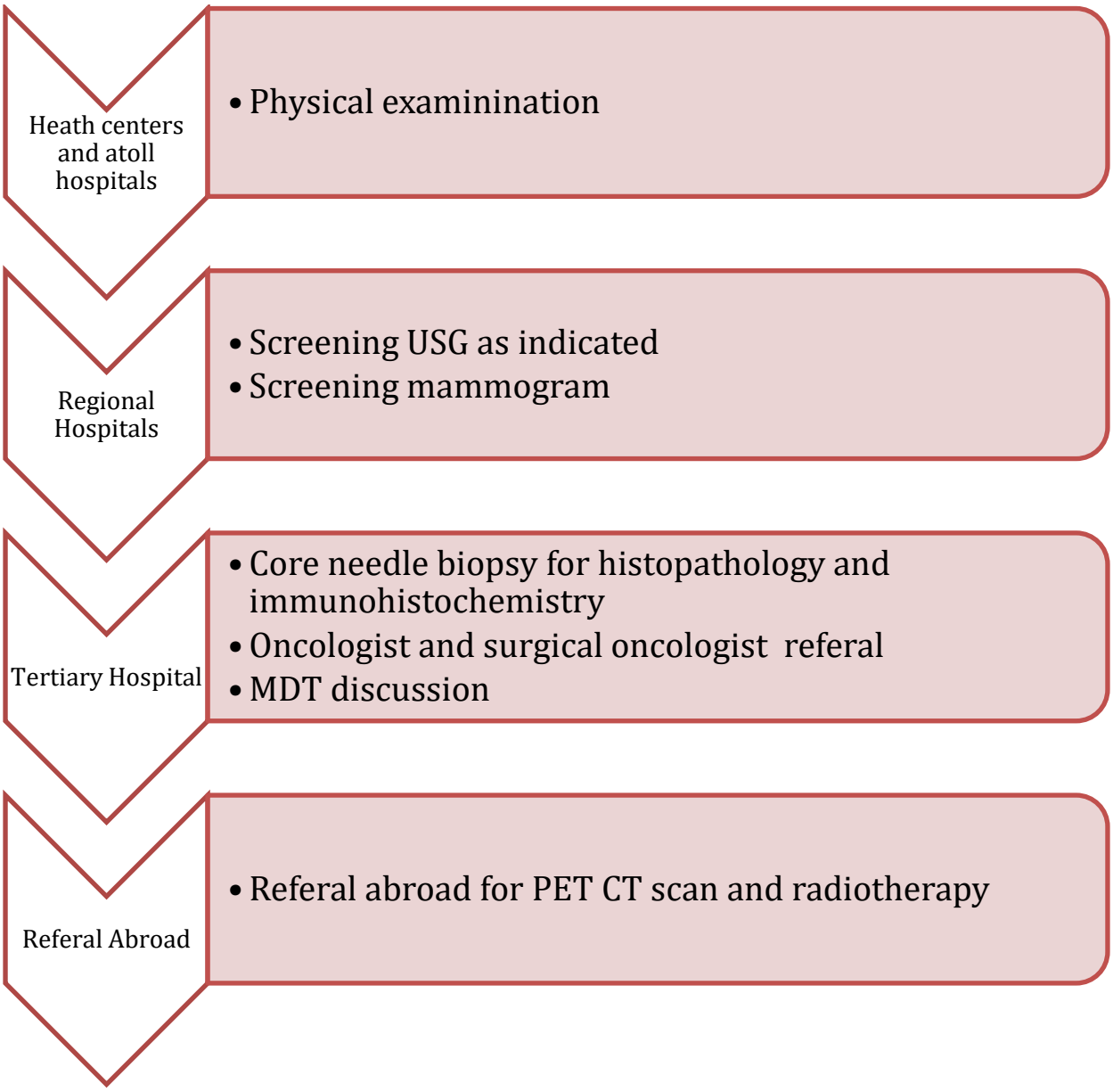
- a palpable breast lump,
- nipple retraction,
- skin dimpling,
- ulceration,
- spontaneous nipple discharge.
- Advanced disease may present with bone pain, cough, or neurological symptoms due to metastasis.

6. Differential Diagnosis

- fibroadenoma
- mastitis
- breast cysts,
- fat necrosis
- Secondary metastatic lesions from extramammary primaries should also be considered

7. Referral Pathways in the Maldives

Patients with suspected or confirmed breast malignancy should be referred from atoll and regional hospitals to Tertiary Hospitals for specialist evaluation. Confirmed cases requiring radiotherapy, complex surgery, or PET-CT are referred to tertiary or overseas centers through the Aasandha mechanism. Multidisciplinary tumor board (MDT) discussion is encouraged for all complex cases.



8. Investigations

- clinical examination
- bilateral mammography
- ultrasound of the breast and axilla

- MRI if indicated
- core biopsy with histopathology and IHC for ER, PgR, HER2, and Ki67.
- Staging investigations follow AJCC TNM classification and include CT, bone scan, or PET-CT for high-risk cases.

9. 1 Early Breast Cancer

a. Screening, Diagnosis, Pathology & Molecular biology

Diagnostic work-up for Early Breast Cancer	
Assessment of general health status	• History • Menopausal status • Physical examination • Full blood count • Liver, renal and cardiac (in patients planned for anthracycline and/or trastuzumab treatment) function tests, alkaline phosphatase and calcium
Assessment of primary tumour	• Physical examination • Mammography • Breast US • Breast MRI in selected cases • Core biopsy with pathology determination of histology, grade, ER, PgR, HER2 and Ki67
Assessment of regional lymph nodes	• Physical examination • US • US-guided biopsy if suspicious
Assessment of metastatic disease	• Physical examination • Other tests are not routinely recommended, unless high tumour burden, aggressive biology or when symptoms suggestive of metastases are present

b. Diagnostic work-up for Early Breast Cancer

Intrinsic subtype	Clinicopathological surrogate definition
Luminal A	Luminal A-like: • ER-positive • HER2-negative • Ki67 low* • PgR high[1] • Low-risk molecular signature (if available)
Luminal B	Luminal B-like (HER2-negative): • ER-positive • HER2-negative and either • Ki67 high or • PgR low or • High-risk molecular signature (if available) Luminal B-like (HER2-positive): • ER-positive • HER2-positive • Any Ki67 • Any PgR

c. Surrogate definitions of intrinsic subtypes of breast cancer

Luminal A and Luminal B

*Ki-67 scores should be interpreted in light of local laboratory values: as an example, if a laboratory has a median Ki-67 score in receptor-positive disease of 20%, values of 30% or above could be considered clearly high; those of 10% or less clearly low.

[1]Suggested cut-off value is 20%; quality assurance programmes are essential for laboratories reporting these results.

HER2 and basal-like

‡There is ~80% overlap between 'triple-negative' and intrinsic 'basal' subtype, but 'triple-negative' also includes some special histological types such as carcinoma with a rich lymphocytic stroma (former medullary), secretory carcinoma, low-grade metaplastic carcinoma and adenoid cystic carcinoma.

Adapted from the 2013 St Gallen Consensus Conference

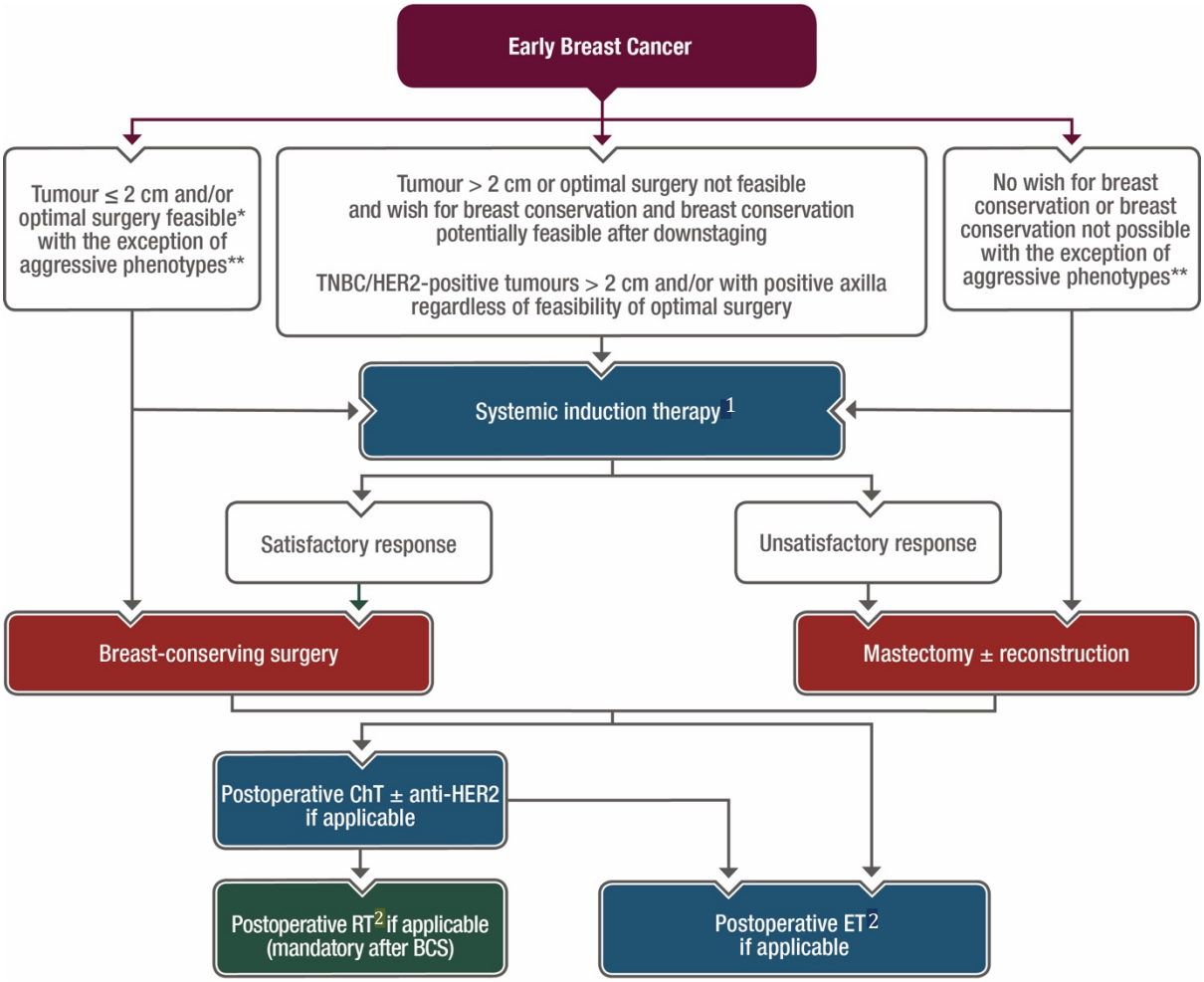
Intrinsic subtype	**Clinicopathological surrogate definition**
HER2	HER2-positive (non-luminal): • HER2-positive • ER and PgR absent
Basal-like	Triplenegative‡: ER and PgR absent‡ HER2-negative‡

d. Staging and risk assessment

Summary of recommendations
Disease stage should be assessed according to the AJCC TNM staging system
Minimum blood work-up is recommended before surgery and systemic (neo)adjuvant therapy, with chest, abdomen and bone imaging for higher-risk patients
Postoperative pathological assessment of surgical specimens should be made according to the pathological TNM system

e. Management

Summary of recommendations
Treatment should be carried out by a specialised breast cancer multidisciplinary team in specialised breast units/centres and patients should be actively involved in all management decisions
Treatment should be based on the tumour burden/location and biology, as well as age, menopausal status, general health status and patient preference
Fertility and fertility-preservation should be discussed with younger premenopausal patients prior to the initiation of any systemic treatment



* Biology that requires ChT (TNBC, HER2-positive, luminal B-like), to assess response and prognosis and eventually decide on postoperative therapies, should preferentially receive preoperative ChT

** Aggressive phenotypes: TNBC or HER2-positive breast cancer

1. If ChT is planned, it should all be given as neoadjuvant

2. Concomitant postoperative RT, postoperative ET and anti-HER2 therapy

f. Surgery

In all women undergoing mastectomy, breast reconstruction should be available, and immediate reconstruction is suitable for the vast majority of cases except inflammatory cancer; the optimal reconstruction technique for each patient should be discussed individually

Type of tumour	Method
Most early breast cancers	BCS is the preferred local treatment option
Early, clinically node-negative breast cancer	• SLNB is the standard of care for axillary staging • If positive SLNB, further axillary surgery is not required for low axillary disease burden, axillary RT is an alternative
DCIS	BCS (with a 2 mm margin) followed by WBRT or total mastectomy are acceptable treatment options
Occult breast cancer	ALND and WBRT are the preferred locoregional management

Summary of recommendations	
Risk-reducing mastectomy	
Very high-risk patients	Risk-reducing surgery may be offered and pre surgery genetic assessment and psychological counselling are mandatory
Non-high-risk patients opting for bilateral mastectomy	should be counselled that survival outcomes with BCS may be better
Surgery after PST	
If BCS is anticipated, the tumour site should be marked and pre- and post-treatment breast MRI carried out	
In clinically negative axilla, post-PST SLNB is preferred to pre-PST SLNB	
SLNB may be carried out in selected cases of baseline limited axillary involvement converting to negative	
Tumour deposits in post-PST SLNB prompt ALND	

g. Local treatment

Risk-reducing mastectomy and Surgery after PST

Type of situation	Indications on RT
Routine postoperative RT	Moderate hypofractionation schedules (15–16 fractions of ≤ 3 Gy/fraction) are recommended
After BCS	Postoperative WBRT is strongly recommended • Boost RT where there is a high risk of local recurrence Accelerated partial-breast RT where the risk of recurrence is low
Post-mastectomy: high-risk patients / patients with 1-3 positive axillary lymph nodes	PMRT is recommended
Patients with involved lymph nodes	Regional comprehensive nodal RT is recommended
After ALND	Routine axillary irradiation should not be applied to the operated part of the axilla
After immediate breast reconstruction	Postoperative RT can be administered, if indicated
In DCIS	WBRT is recommended for most women undergoing BCS, with tumour bed boost being a consideration for patients at a high risk of local failure

h. Radiation Treatment

Subtype	Recommended therapy	Comments
Luminal A-like	ET alone in the majority of cases	Consider ChT if high tumour burden (≥ 4 LNs, T3 or higher)
Luminal B-like (HER2-negative)	ChT followed by ET for the majority of cases	-
Luminal B-like (HER2-positive)	ChT + anti-HER2 followed by ET for all patients	If contraindications for the use of ChT, one may consider ET + anti-HER2 therapy, although no randomised data exist
HER2-positive (non-luminal)	ChT + anti-HER2	-
Triple-negative (ductal)	ChT	-

i. Systemic treatment

Recommendations for early breast cancer subtypes

For special histological types, the authors recommend following the St Gallen recommendations that propose ET for endocrine-responsive histologies (cribriform, tubular and mucinous), ChT for high-risk endocrine- nonresponsive histologies (medullary, metaplastic) and no systemic therapy for low-risk endocrine nonresponsive histologies (adenoid cystic and apocrine)

Biomarker	Method	Use
ER	IHC Positive if ≥ 1%	Essential to the characterization of the IHC luminal-like group Poor prognostic marker if negative Predictive marker for ET Mandatory for ET prescription
PgR	IHC Positive if ≥ 1%	If negative tumour classified as IHC luminal B-like Strong poor prognostic marker if negative Predictive marker for ET
HER2	IHC Positive if > 10% complete membrane straining (3+) ISH • Single probe if HER2 ≥ 6 copies • Dual probe Positive if HER2/CEP17 ≥ 2 and HER2 copies ≥ 4 or HER2/CEP17 < 2 and HER2 copies ≥ 6	Essential to the characterization of: • HER2-enriched (ER-negative) • Luminal B-like, HER2-positive Prognostic marker Predictive marker of anti-HER2 treatment Mandatory for anti-HER2 therapy regardless of treatment line

(Neo)Adjuvant systemic treatment

Summary of biomarkers used in treatment- decision making – ER, PgR, HER2

Biomarker	Method	Use
Ki67	IHC No final consensus on cut-off but values below 10% are considered low and above 30% are considered high*	Absence of international consensus for scoring and threshold Prognostic value in ER-positive, HER2-negative tumours (primary tumours and post-neoadjuvant residual tumour) Absence of prognostic value in HER2-positive or triple-negative tumours Predictive of response to neoadjuvant ET[1] Predictive of response to neoadjuvant ChT If elevated, ChT is often prescribed in ER-positive, HER2-negative tumours Part of the IHC definition of luminal-like tumours • Ki67 low, luminal A-like • Ki67 high, luminal B-like
Intrinsic subtypes	Gene expression profile, N-CounterTM technology	Prognostic Predictive: Different responses to neoadjuvant ChT and anti-HER2 therapy according to the subtype

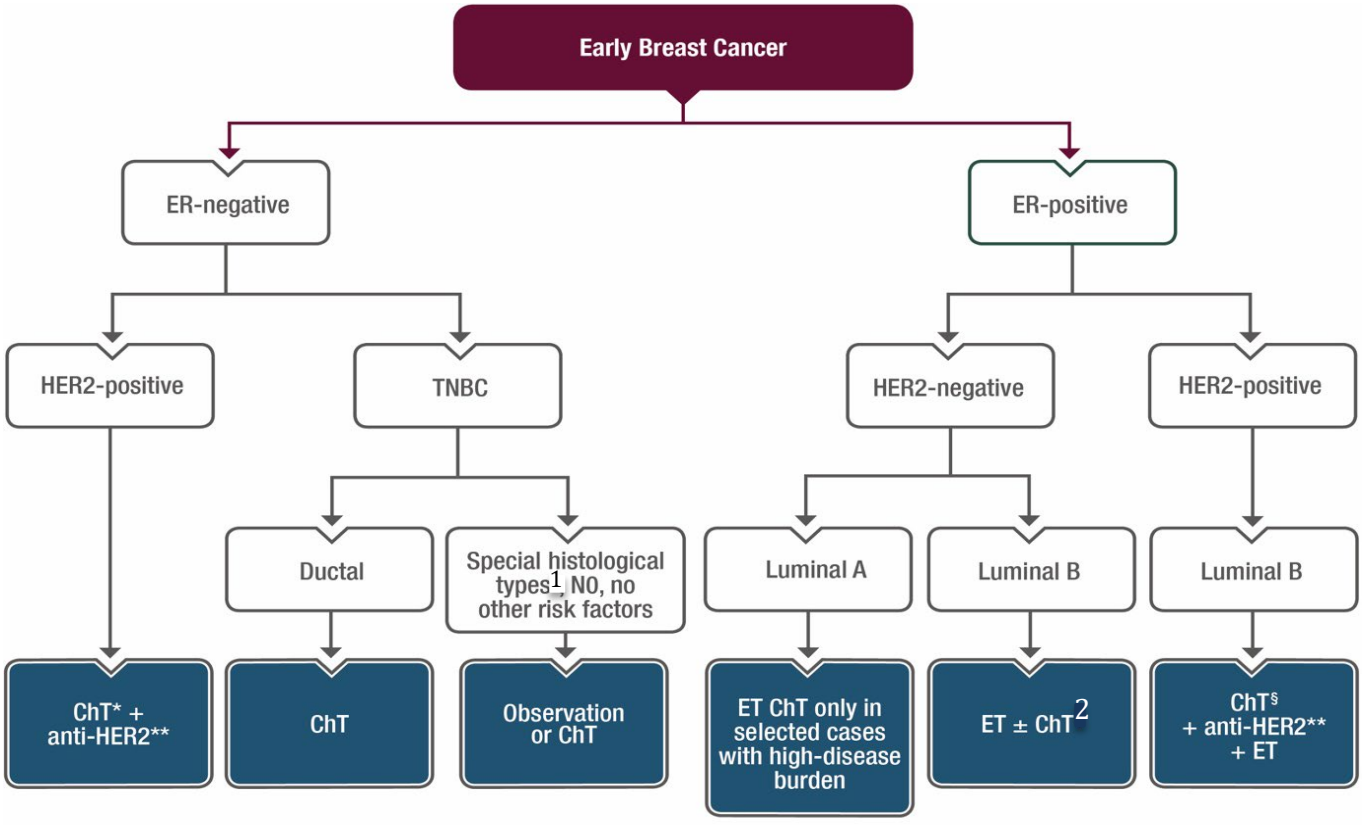
Summary of biomarkers used in treatment- decision making – Ki67, intrinsic subtypes

* According to the International Ki67 Working Group Guidelines, Dowsett M et al. J Natl Cancer Inst 2011;103:1656–64.

[1] A decrease in Ki67 expression during neoadjuvant ET is highly predictive of response

Biomarker	Method	Use
First-generation signatures (MammaPrint, Oncotype DX)	Gene expression profile, RT-PCR	For ER-positive, HER2-negative tumours Prognostic (Neo)Adjuvant ChT is indicated if high risk or high score Can be carried out in biopsy or surgical specimen
Second-generation signatures (Prosigna®, Endopredict®)	N-CounterTM technology, RT-PCR	For ER-positive, HER2-negative tumours, include T size and N status in their final score Prognostic (Neo)Adjuvant ChT is indicated if high risk or high score Can be carried out in biopsy or surgical specimen

Summary of biomarkers used in treatment- decision making – First and second- generation signatures



Treatment choice by marker expression and intrinsic phenotype (Neo)-adjuvant systemic treatment choice by marker expression and intrinsic phenotype.

* With possible exception of selected cases with very low risk T1abN0.

** Anti-HER2: trastuzumab ± pertuzumab.

1 Adenoid cystic or apocrine, secretory carcinoma, low-grade metaplastic carcinoma.

2 Depending on level of ER and PgR expression, proliferation, genomically assessed risk, tumour burden and/or patient preference.

§ Except for very low-risk patients T1abN0 for whom ET/anti-HER2 therapy alone can be considered.

Summary of recommendations
• **Adjuvant treatment should start within 3–6 weeks after surgery** • **Neoadjuvant treatment should start within 2–4 weeks of diagnosis and staging**
All luminal-like cancers should be treated with ET
ChT: • **not required for most luminal A-like tumours** • **not concomitantly with ET, except for gonadotropin-releasing hormone analogues used for ovarian protection** • **use based on risk of recurrence and presumed responsiveness to ET (for luminal B-like HER2-negative)** • **with anti-HER2 therapy and followed by ET (for luminal B-like HER2-positive)**
Patients with TNBC should generally receive ChT
HER2-positive cancers should generally be treated with ChT plus anti-HER2 therapy
Anti-HER2 therapy may routinely be combined with non-anthracycline-based ChT, ET and RT, and should be administered sequentially to anthracycline-based ChT
RT may be delivered safely during anti-HER2 therapy, ET and non-anthracycline, non-taxane-based ChT
When used together, ChT should usually precede RT

Summary of recommendations	
Premenopausal patients	• Tamoxifen for 5–10 years is standard, AI alternative for high-risk patients (if AI is given, OFS/OA is mandatory) • Patients becoming postmenopausal during the first 5 years of tamoxifen, can be switched to letrozole • Patients < 35 years not requiring ChT should receive OFS combined with ET
Postmenopausal patients	• AIs (upfront, after tamoxifen or as extended adjuvant therapy) and tamoxifen are standard treatments • There is only a minimal benefit for the use of AIs for more than 5 years

Summary of recommendations
ChT should be administered for 12–24 weeks (4–8 cycles) • **Sequential anthracycline (EC or AC)/taxane-based regimen is the standard** • **4 cycles of anthracycline- or taxane-based ChT or CMF may be used in lower-risk patients**
Non-anthracycline regimens may be used in patients at risk of cardiac complications
G-CSF-supported dose-dense schedules should be considered, particularly in highly proliferative tumours

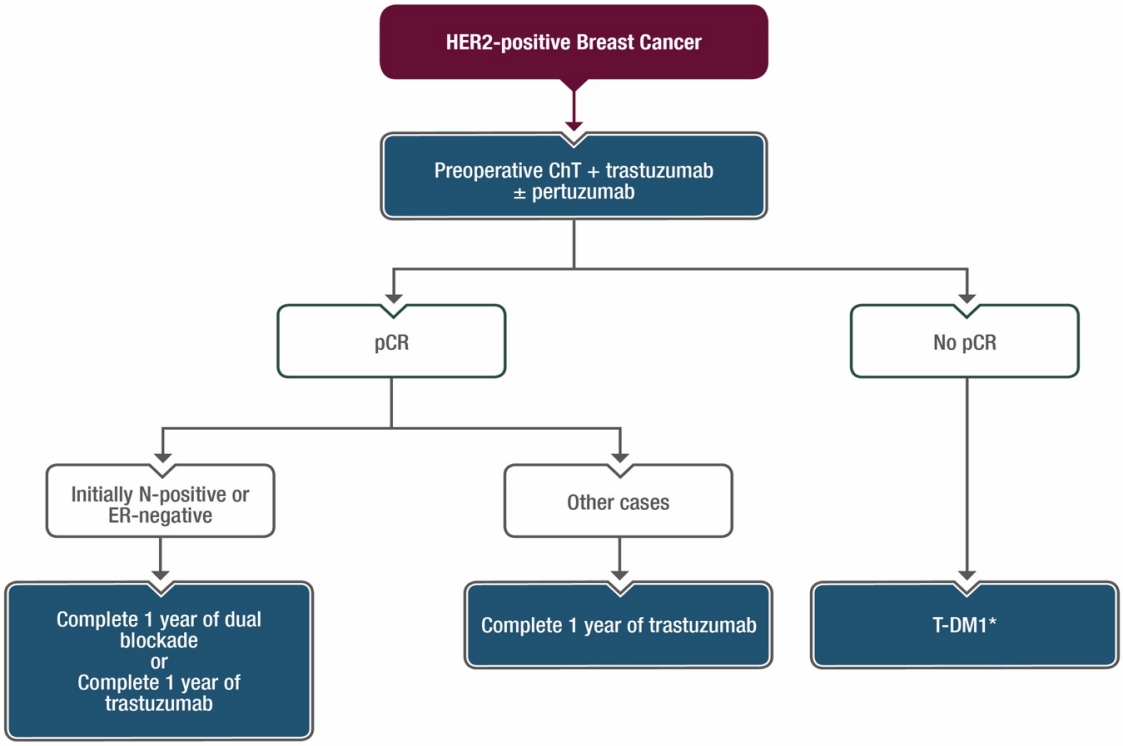
Chemotherapy

Summary of recommendations
Standard is: one year of (neo)adjuvant trastuzumab for HER2-positive patients with no contraindications
Trastuzumab can be given concomitantly with non-anthracycline-based (sequentially with anthracycline-based) ChT
Regular cardiac monitoring before starting and during trastuzumab treatment is mandatory
High-risk patients:

- **One year of combined trastuzumab/pertuzumab can be considered**
- **Extended anti-HER2 therapy with neratinib may be considered in some cases**

If residual invasive disease after combined neoadjuvant ChT and anti-HER2 therapy, adjuvant trastuzumab should be replaced by adjuvant T-DM1

Anti-HER2 therapy



HER2-positive breast cancer treatment

* Not EMA-approved

Type of situation	Treatment
• Locally advanced and large operable cancers • Tumours > 2 cm requiring ChT	PST recommended
Most patients	Sequential anthracyclines and taxanes recommended
TNBC or *BRCA1/2*-mutated disease	Sequential anthracyclines + taxanes +/- platinum
Postmenopausal patients with ER-positive/HER2-	Preoperative ET should be considered and

negative cancers requiring PST	continued postoperatively
• Women with low-oestrogen status • Women with treatment-related bone loss	Bisphosphonates are recommended, especially if at high risk of relapse

Type of situation	Treatment
Elderly patients	Treatment should be adapted to biological age: • Standard multidrug regimen recommended for suitable patients • Less aggressive regimen recommended for frail patients
Male breast cancer patients	• Standard adjuvant ET is tamoxifen • An AI alone should not be used; if needed, combine with LHRH analog
Both males and females	Same ChT/anti-HER2 therapy indications and regimen recommendations
DCIS	Both tamoxifen and AIs may be used after conservative local treatment and after mastectomy

j. Other clinical scenarios

Summary of recommendations
ER, PgR and HER2 status should guide all systemic treatment decisions
Surrogate intrinsic tumour phenotypes, based on expression of ER, PgR, HER2 and Ki67, should be used to define subpopulations of breast cancers
Expression of uPA-PAI1 or validated multigene panels may be used in conjunction with clinicopathological factors to guide challenging systemic treatment decisions

k. Follow- up

1. Clinical Evaluation

- **History and physical examination:**
  - Every **4–6 months for the first 5 years** after completion of active therapy (surgery ± adjuvant therapy).
  - **Annually thereafter** for life.

- Assess for:
    - New breast or chest-wall symptoms, bone pain, cough, dyspnea, neurological or systemic complaints.
    - Treatment-related toxicities (e.g. lymphedema, cardiotoxicity, menopause-related symptoms).
    - Psychosocial issues, fatigue, sexual health, fertility, and menopausal symptoms.

2. Imaging Surveillance

- **Annual bilateral mammography** (and **breast ultrasound [USG]** where indicated):
    - Start **6–12 months after completion of radiotherapy** (or 12 months after the last pre-operative mammogram if no RT).
    - Continue **annually** for life.
- **Breast ultrasound (USG)** should be used as a **complementary modality**—especially for:
    - Dense breasts, young women (< 40 years), or inconclusive mammogram results.
    - Post-surgical sites with scarring where mammogram sensitivity is reduced.
- **MRI breast** is reserved for selected high-risk patients (e.g. BRCA1/2 mutation carriers, strong family history).
- **Routine systemic imaging** (CT, PET-CT, bone scan) is **not recommended** for asymptomatic patients with no clinical suspicion of recurrence.

3. Laboratory Investigations

- **Not routinely indicated** in asymptomatic patients.
- CBC, renal, and liver function tests only if clinically warranted or if on ongoing systemic therapy (e.g. endocrine or HER2-targeted therapy).
- **Tumor markers (CEA, CA 15-3)** are **not recommended** for routine surveillance (NCCN Category 2B).

4. Endocrine Therapy Monitoring

- For patients on **tamoxifen or aromatase inhibitors (AIs):**
    - Monitor adherence, menopausal symptoms, bone and cardiovascular health.
    - **Bone mineral density (DEXA scan)**: baseline and **every 2 years** for patients on AIs or ovarian suppression.

- Consider calcium/vitamin D supplementation and bisphosphonate therapy as indicated.

5. Cardiac Monitoring

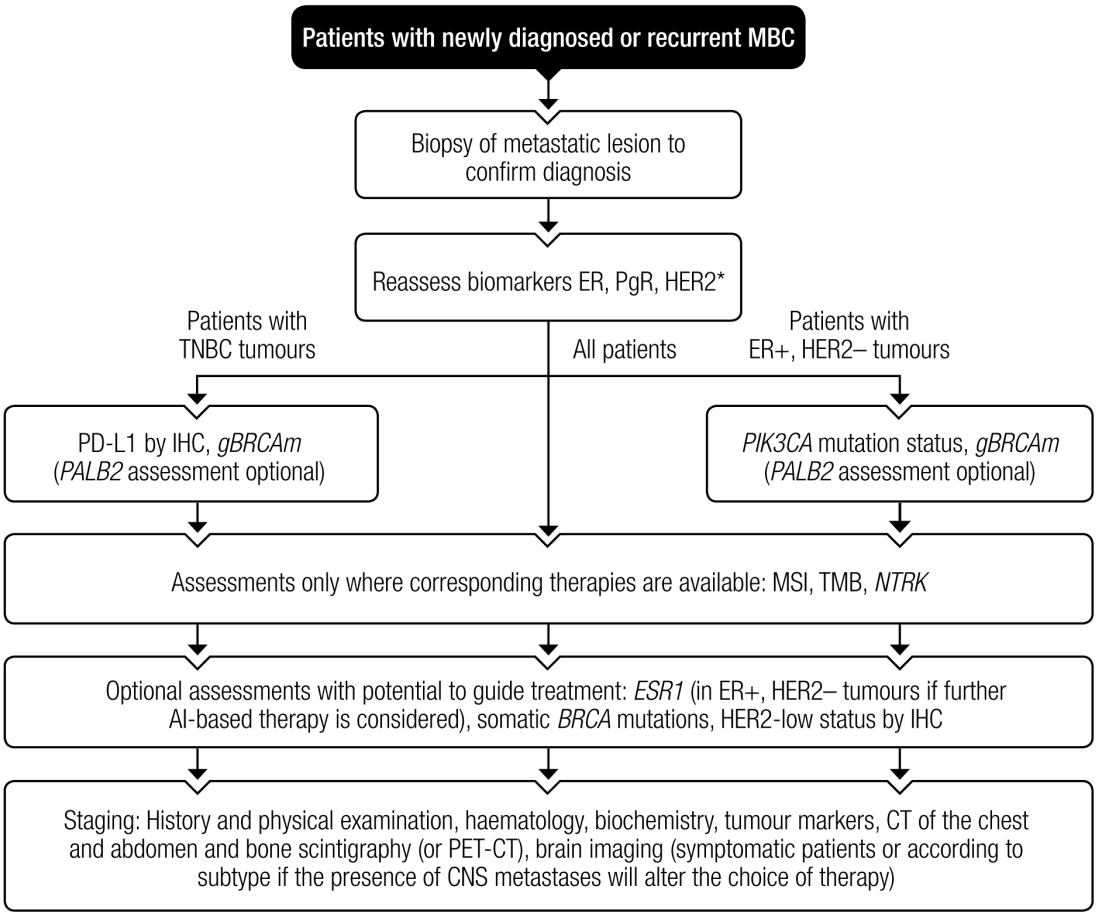
- For patients treated with **anthracyclines** or **HER2-targeted therapy (trastuzumab, pertuzumab):**
  - **Echocardiogram or MUGA scan** at baseline, during treatment, and as clinically indicated thereafter (typically every 6–12 months if ongoing anti-HER2 therapy).

6. Psychosocial and Lifestyle Support

- Encourage physical activity, weight management, healthy diet, and avoidance of tobacco/alcohol.
- Provide psychosocial counseling, support group referral, and fertility counseling where appropriate.
- Address sexual health, cognitive function, and return-to-work guidance.

9.2 Metastatic Breast Cancer

a. Diagnostic work-up and staging of MBC



*If there are important differences in ER, PgR and HER2 status between the primary tumour and recurrence, patients should be managed according to receptor status of the recurrent disease biopsy

- AI, aromatase inhibitor; CNS, central nervous system; CT, computed tomography; ER, oestrogen receptor; *ESR1*, oestrogen receptor 1; *gBRCAm*, germline *BRCA1/2* mutation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MBC, metastatic breast cancer;
- MSI, microsatellite instability; *NTRK*, neurotrophic tyrosine receptor kinase; *PALB2*, partner and localiser of *BRCA2*; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PgR, progesterone receptor; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TMB, tumour mutation burden; TNBC, triple-negative breast cancer

- Patients with newly diagnosed or recurrent MBC should have a biopsy to confirm the histology and assess oestrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) status
- Biopsies of bone metastases should be avoided due to the technical limitations of biomarker detection in decalcified tissue
- If there are important differences in ER, PgR and HER2 status between the primary tumour and recurrence, it is not known which biological features should drive treatment decision making
- The biological features of the disease at baseline, degree of biomarker heterogeneity, type of treatment received that could potentially induce a selection of clones resistant to a specific targeted therapy and the burden of disease should all be considered
- Tumour heterogeneity should be considered for each new line of treatment; a re-biopsy may be appropriate in cases of mixed response
- Other therapeutically-relevant biomarkers that should be assessed include:
- Germline *BRCA1/2* mutation *(gBRCAm)* status in HER2-negative MBC
- Programmed death-ligand 1 (PD-L1) status in triple-negative breast cancer (TNBC)
- Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha *(PIK3CA)* in ER/PgR-positive, HER2-negative MBC
- Genomic profiling and further diagnostic tests (e.g. on tumour tissue or circulating tumour DNA) should only be carried out if the result will change the treatment approach or if the patient can access an appropriate clinical trial

The following should be evaluated when corresponding therapies are available:

- Microsatellite instability (MSI)
- Tumour mutation burden
- Neurotrophic tyrosine receptor kinase *(NTRK)* fusion

b. Staging and Risk Assessment

- Imaging work-up for staging should include computed tomography (CT) of the chest/abdomen and bone scintigraphy
- [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET)-CT may be used as an alternative to CT and bone scans

- The imaging modality chosen at baseline should also be used for disease monitoring to ensure comparability
- There is no evidence that any staging or monitoring approach provides an overall survival (OS) benefit over any other
- The interval between imaging and the start of treatment should be ≤ 4 weeks
- Evaluation of response should be every 2-4 months, depending on disease dynamics, location, extent of metastasis and type of treatment
- Disease monitoring intervals should not be shortened as this does not provide an OS benefit, but may cause emotional and financial harm
- Less frequent monitoring is acceptable, particularly for indolent disease
- If disease progression is suspected, additional tests should be carried out in a timely manner, irrespective of the planned intervals
- Repeat bone scans are a mainstay of evaluation for bone-only/predominant metastases
- Image interpretation may be confounded by a possible flare during the first few months of treatment
- PET-CT might provide earlier guidance in monitoring bone-only or bone-predominant metastases, but prospective trials are needed to study the impact on treatment decisions and OS
- Magnetic resonance imaging (MRI) is recommended for suspected cord compression
- Brain imaging should not be routinely carried out in all asymptomatic patients at initial MBC diagnosis or during disease monitoring
- Patients with asymptomatic HER2-positive disease or TNBC have higher rates of brain metastases (BMs) at initial MBC diagnosis, which may warrant subtype-oriented brain imaging if detection of central nervous system (CNS) metastases will affect the choice of systemic therapy
- Symptomatic patients should always undergo brain imaging, preferably with MRI

c. Treatment

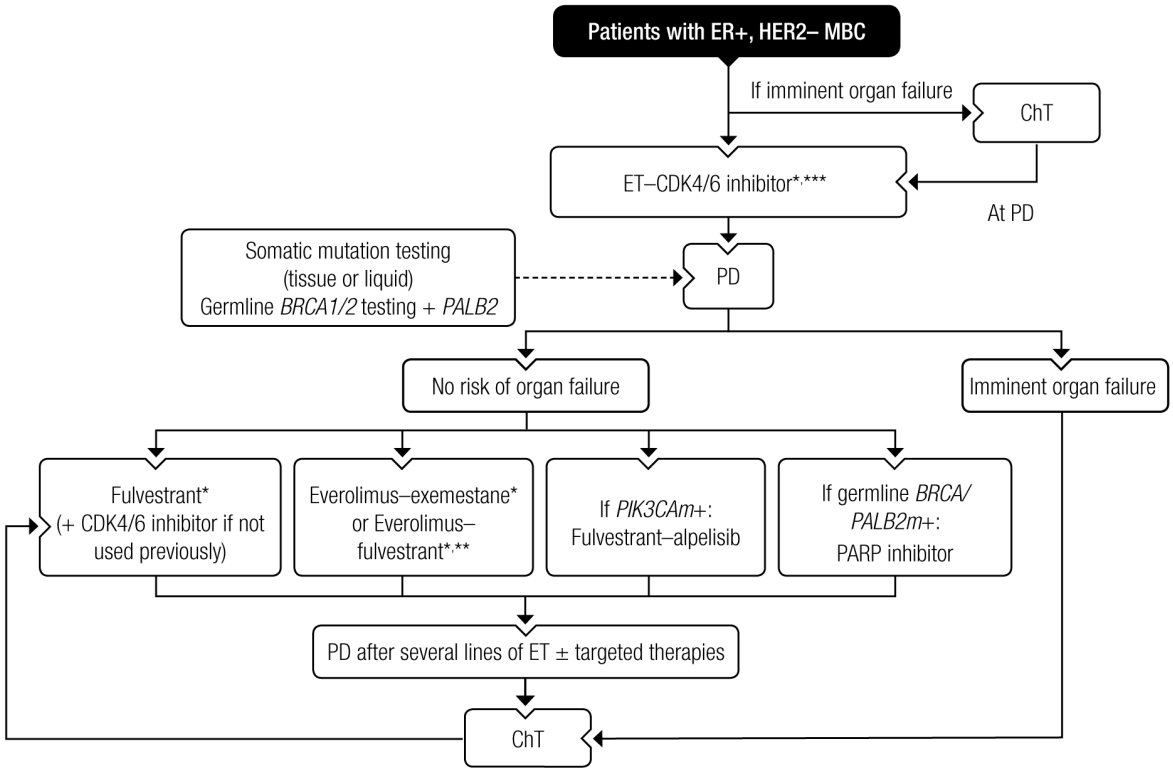
- Systemic therapy is the standard of care in MBC but may be supplemented with locoregional treatments (LRTs) according to the disease status of the individual patient
- A multidisciplinary team is a prerequisite for optimal management
- Treatment decisions should be made irrespective of patient age, but comorbidities, patient characteristics and patient preferences need to be considered
- Rechallenge with drugs previously used in the early breast cancer (BC) setting is a reasonable option, provided that the disease-free interval (DFI) is ≥ 12 months after the last drug administration and that no toxicities remain

- Patients with MBC should be encouraged to consider participation in clinical trials early in their disease course

d. Luminal Breast Cancer

Management options for ER-positive, HER2-negative MBC are shown in the figure below

MANAGEMENT OF ER-POSITIVE, HER2-NEGATIVE MBC



*OFS if the patient is premenopausal

**Preferred if the patient is *ESR1* mutation positive

***If relapse < 12 months after end of adjuvant AI: Fulvestrant–CDK4/6 inhibitor*; if relapse > 12 months after end of adjuvant AI: AI–CDK4/6 inhibitor*

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4 and 6; ChT, chemotherapy; ER, oestrogen receptor; *ESR1*, oestrogen receptor 1; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; m, mutation; MBC, metastatic breast cancer; OFS, ovarian function suppression; *PALB2*, partner and localiser of *BRCA2* ; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

- Premenopausal women may be treated in the same way as postmenopausal women, providing they undergo ovarian function suppression (OFS) or ovarian ablation
- If a rapid response is required, bilateral oophorectomy may be preferable over gonadotropin-releasing hormone agonists
- Primary endocrine resistance is defined as: Relapse during the first 2 years of adjuvant endocrine therapy (ET)
- Progressive disease (PD) within the first 6 months of first-line ET for MBC
- Secondary (acquired) resistance is defined as: Relapse during adjuvant ET but after the first 2 years or Relapse within 12 months of completing adjuvant ET or PD 6 months after initiating ET for MBC

First Line Treatment

- A cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor combined with ET is the standard of care first-line therapy for patients with ER-positive, HER2-negative MBC
- Aromatase inhibitor (AI)–CDK4/6 inhibitor is recommended for patients who did not relapse on an AI or within 12 months of stopping adjuvant AI
- Fulvestrant–CDK4/6 inhibitor is recommended for patients who relapsed on adjuvant AI therapy or within 12 months of stopping adjuvant AI
- ET alone in the first-line setting should be reserved for patients with comorbidities or a performance status that precludes the use of CDK4/6 inhibitor combinations

Second line Treatment

- The optimal sequence of endocrine-based therapy after progression on CDK4/6 inhibitors is uncertain
- Treatment choice depends on prior therapy, duration of response to prior ET, disease burden, patient preference and treatment availability
- In patients who required first-line chemotherapy (ChT) due to imminent organ failure, or who did not have access to a CDK4/6 inhibitor in the first-line setting, ET–CDK4/6 inhibitor is acceptable as subsequent therapy

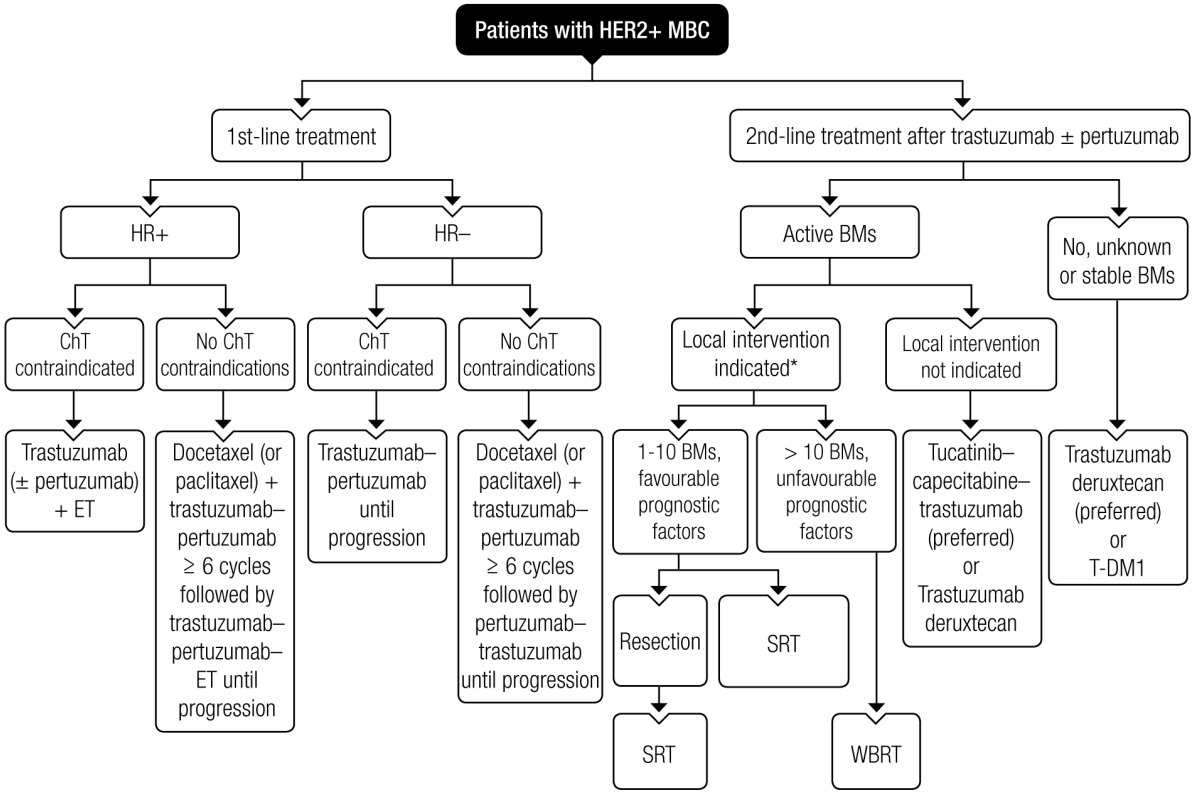
- Determination of somatic *PIK3CA* and oestrogen receptor 1 *(ESR1)* mutations, as well as germline *BRCA1/2* and partner and localiser of *BRCA2 (PALB2)* mutations, is recommended in patients who relapse after ET–CDK4/6 inhibitor
- The choice of second-line therapy (ChT versus endocrine-based therapy) should be based on disease aggressiveness, extent and organ function, and should consider the associated toxicity profiles
- Fulvestrant–alpelisib is an option for patients with *PIK3CA*-mutant tumours, prior exposure to an AI (± CDK4/6 inhibitor) and appropriate glycated haemoglobin levels
- Hyperglycemia can occur with Alpelisib so collaboration with a diabetes specialist is recommended
- Everolimus–exemestane is a second-line treatment option
- Capecitabine is a good alternative in patients unlikely to tolerate everolimus–exemestane
- Tamoxifen or fulvestrant can also be combined with everolimus
- Stomatitis prophylaxis must be used during everolimus treatment
- A poly (ADP-ribose) polymerase (PARP) inhibitor (olaparib or talazoparib) should be considered for patients with germline pathogenic *BRCA1/2* mutations and is an option for patients with somatic pathogenic (or likely pathogenic) *BRCA1/2* or germline *PALB2* mutations
- At least two lines of endocrine-based therapy are preferred before moving to ChT
- In patients with imminent organ failure, ChT is preferred

e. Her2 Breast Cancer

First- and second-line management

options for HER2-positive MBC are shown in the figure below

FIRST- AND SECOND-LINE TREATMENT OF HER2-POSITIVE MBC



*Keep on current systemic therapy unless PD outside CNS

BM, brain metastasis; ChT, chemotherapy; CNS, central nervous system; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; PD, progressive disease; SRT, stereotactic radiotherapy; T-DM1, ado-trastuzumab emtansine; WBRT, whole brain radiotherapy

- The gold-standard first-line treatment for HER2-positive MBC is trastuzumab–pertuzumab–docetaxel, regardless of hormone receptor (HR) status
- Docetaxel should be given for at least 6 cycles, if tolerated, followed by maintenance trastuzumab–pertuzumab until PD
- An alternative taxane (e.g. paclitaxel or nab-paclitaxel) may be used
- ET may be added to trastuzumab–pertuzumab maintenance therapy for HER2-positive, HR-positive tumours
- OFS should be added for pre- and perimenopausal women
- In patients with HER2-positive, HR-positive disease who are not suitable for first-line ChT, ET (e.g. an AI) with HER2-targeted therapy (e.g. trastuzumab, trastuzumab–pertuzumab, trastuzumab–lapatinib or lapatinib), may be recommended

- Single-agent ET without HER2-targeted therapy is not routinely recommended unless comorbidities (e.g. cardiac disease) preclude the safe use of HER2-directed therapies
- If ChT is contraindicated in patients with HER2-positive, HR-negative disease, HER2-targeted therapy without ChT (e.g. trastuzumab or trastuzumab–pertuzumab) may be used
- If taxanes are contraindicated, a less toxic ChT partner may be considered (e.g. capecitabine or vinorelbine)
- Patients with metastatic recurrence within 6-12 months of receiving adjuvant trastuzumab–pertuzumab should follow second-line therapy recommendations
- Patients with distant metastatic recurrence within 12 months of adjuvant trastuzumab (without pertuzumab) may receive first-line trastuzumab–pertuzumab–taxane or second-line therapy

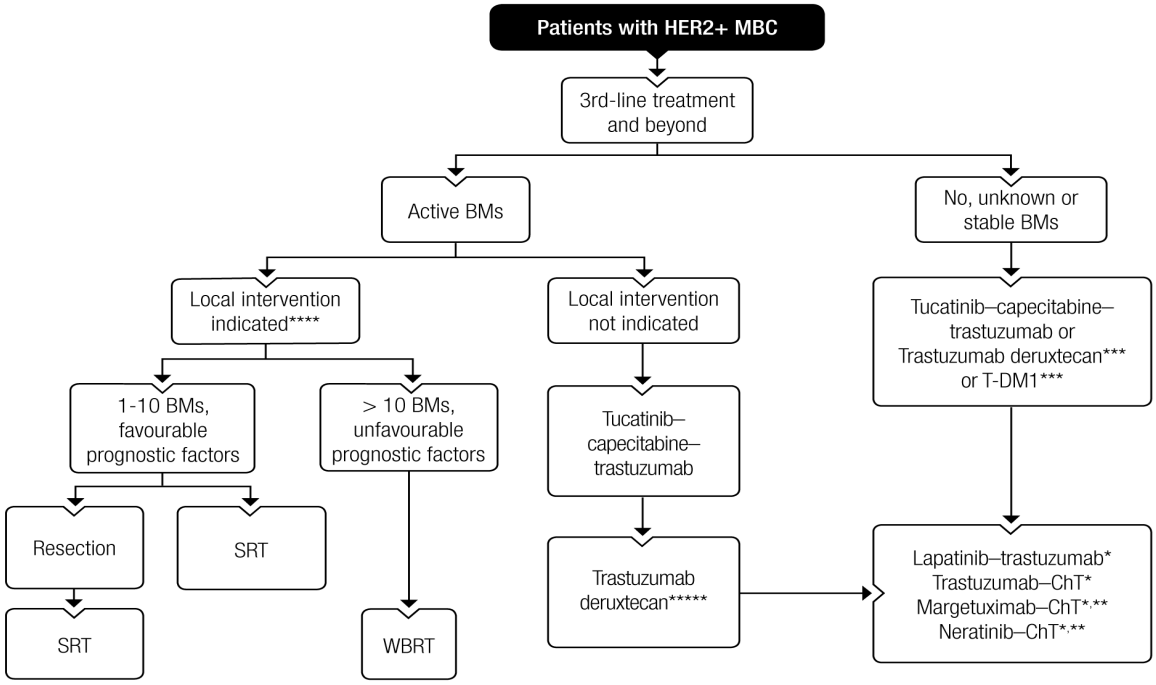
Second Line Treatment

- Trastuzumab deruxtecan is the preferred second-line therapy after progression on a taxane and trastuzumab
- If trastuzumab deruxtecan is not available, ado-trastuzumab emtansine (T-DM1) is an option
- In selected patients with BMs, second-line tucatinib–capecitabine–trastuzumab or trastuzumab deruxtecan may be used

Third Line Therapy

Third- and further-line management options for HER2-positive MBC are shown in the figure on the next page

THIRD-LINE AND BEYOND TREATMENT OF HER2-POSITIVE MBC



*There are no data for any of these combinations after tucatinib- and/or trastuzumab deruxtecan-based therapy

**FDA approved, not EMA approved

***If not received as second-line therapy

****Keep on current systemic therapy unless PD outside CNS

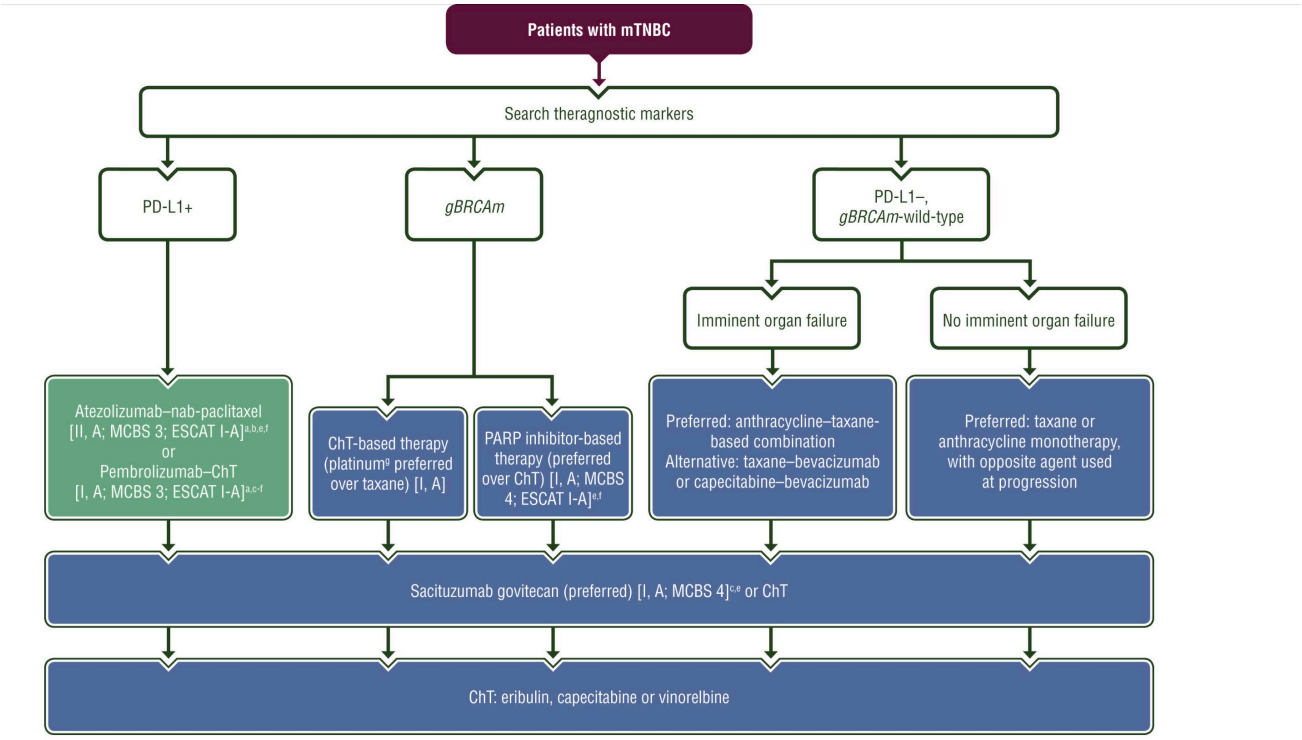
*****If not previously used, including all other drugs that are also a second-line treatment option

BM, brain metastasis; ChT, chemotherapy; CNS, central nervous system; EMA, European Medicines Agency; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; PD, progressive disease; SRT, stereotactic radiotherapy; T-DM1, ado-trastuzumab emtansine; WBRT, whole brain radiotherapy

- The choice of third-line treatment depends on prior second-line therapy, patient characteristics, toxicity profiles and availability
- The most active treatment options appear to be tucatinib–capecitabine–trastuzumab, trastuzumab deruxtecan and T-DM1
- In later lines of therapy, lapatinib is an option to be used preferably in combinations (e.g. with capecitabine, trastuzumab or ET)
- Neratinib and margetuximab can be considered for late-line treatment

- The most appropriate setting might be in patients who have exhausted all standard therapy options; however, there is no evidence for sequencing a tyrosine kinase inhibitor (TKI) after a TKI
- Continued anti-HER2-based therapy is the current standard for patients with HER2- positive tumours
- If other anti-HER2 therapies have been exhausted, are not considered suitable or are not available, sequential trastuzumab-based strategies (in combination with different ChTs) beyond progression should be considered

f. Triple Negative Breast Cancer



g. Follow-Up for Metastatic Breast Cancer

(Adapted from NCCN 2025)

1. Clinical Evaluation

- **Every 2–4 months** during active systemic therapy (e.g. chemotherapy, targeted, or endocrine therapy).
- **Every 3–6 months** for patients with stable disease on maintenance or endocrine therapy alone.

- **Every 4–12 weeks** for those on newly initiated systemic therapy until stable.
- **At each visit**, assess:
    - Performance status (ECOG)
    - Treatment tolerance and toxicity
    - Weight, vitals, and symptom review (pain, fatigue, dyspnea, neurological symptoms, etc.)
    - Physical examination, emphasizing breast/chest wall, nodal areas, liver, bones, and any known metastatic sites

2. Laboratory Tests

- **CBC, renal and liver function tests** every 2–3 cycles during chemotherapy, then as clinically indicated.
- **Tumor markers (CA 15-3, CEA)** *may be considered* for monitoring if previously elevated, but should **not be used alone** to make treatment decisions (NCCN Category 2B).
- **Electrolytes, glucose, lipid profile** as required for patients on targeted agents (e.g. alpelisib, everolimus).

3. Imaging

- **Frequency:**
    - **Every 2–4 months** initially to assess response (depending on disease burden and therapy type).
    - **Every 3–6 months** for stable patients on long-term treatment.
    - **Earlier** if new symptoms suggest progression.
- **Modality:**
    - CT chest/abdomen/pelvis or PET-CT (use the same modality throughout follow-up for consistency).
    - MRI brain if neurologic symptoms arise or in HER2-positive or TNBC subtypes at high CNS risk.
    - Bone scan or PET-CT for bone-predominant disease; note possible flare phenomenon in early therapy phase.

4. Supportive and Palliative Care

- **Integrate symptom management** and palliative care early in the disease course.
- **Bone health:** Evaluate for bone-modifying agents (zoledronic acid or denosumab); dental review prior to initiation.
- **Cardiac monitoring:**
    - Baseline and **every 3–6 months** for patients on HER2-targeted therapy or anthracyclines.
- **Psychosocial assessment:** screen for anxiety, depression, and caregiver stress regularly.

5. Survivorship and End-of-Life Planning

- Transition to less intensive monitoring when the disease becomes refractory or patient is in palliative-only phase.
- Discuss goals of care, advanced directives, and hospice options as appropriate.

10. Screening

Breast cancer screening remains one of the most effective strategies for early detection and improved survival. In the Maldivian context, where breast cancer incidence is rising and a proportion of cases present at advanced stages, organized screening and public awareness are essential public health priorities.

a. Recommended Screening Modalities

- **Mammography and Ultrasound (USG):**
  Bilateral mammography combined with targeted breast ultrasound (USG) is recommended as the standard screening approach.
    - For **average-risk women aged 50–69 years**, screening should be performed **every two years**.
    - For **women aged 40–49 years**, screening may be offered based on individual risk assessment, family history, and clinical judgment.
    - For **women aged 70 years and older**, continued screening should be individualized based on life expectancy and comorbidities.

- **High-risk women** (e.g. carriers of BRCA1/2 or strong family history) should undergo **annual breast MRI** in addition to mammography and/or USG, beginning at age 30, or earlier depending on genetic counseling recommendations.
- **Breast ultrasound (USG)** serves as a complementary tool to mammography, especially for dense breast tissue, young women, and when mammography results are inconclusive or contraindicated.

b. Opportunistic and Clinical Screening

- Routine **clinical breast examinations (CBE)** should be integrated into primary healthcare services at all regional and atoll levels.
- Healthcare workers should be trained to recognize suspicious breast changes and promptly refer patients to diagnostic centers (IGMH or Tree Top Hospital).

c. Public Awareness

Public education campaigns emphasizing breast self-awareness, early presentation, and adherence to national screening recommendations should be implemented through the National Cancer Control Programme and community health platforms.

11. Implementation and Evaluation

Implementation will involve national rollout via the Ministry of Health and National Cancer Control Programme. Training workshops for clinicians, nurses, and allied health professionals will ensure uniform application. Guideline compliance, patient outcomes, and service utilization will be reviewed annually to guide updates.

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