ADVANCED/METASTATIC BREAST CANCER

➢ Acknowledgement

- We would like to acknowledge the Oncology Committee of Egyptian health council (EHC) Guidelines and Breast Cancer Scientific Committee, for adapting this Guidelines.
- Chair of the Committee of Egyptian health council Guidelines: Prof Hussein Khaled.
- The Oncology Committee Members: Ebtesam Saad Eldin, Ehab Khalil, Emad Hamada, Fouad Abuotaleb, Hesham Elghazaly, Hesham Tawfik, Khaled Abdelkarim, Lobna ezz Elarab, Mary Gamal, Mohamed Abdel Mooti, Mohamed Gamil, Nervana Hussein, Ola Khorshid, Omar Sherif Omar, Rasha Fahmi, Rasha Shaltout, Samir Shehata, Yousri Wasef & Yousri Rostom.
- The Breast Cancer Scientific Committee Members: Mohamed Gamil, Lobna Ezz Elarab, Hesham Elghazaly, Ehab Khalil, Rasha Fahmi, Rasha Shaltout, Omar Sherif Omar.

➢ Abbreviations:

AI Aromatase inhibitor

AJCC American joint committee on cancer

Ax Axilla

BC Breast cancer

BCT Breast conserving therapy

BCS Breast conserving surgery

Bx Biopsy

CEM Contrast-enhanced mammography

CT Chemotherapy

EBC Early breast cancer

ECOG The Eastern Cooperative Oncology Group

EMR Electronic medical records

ESMO European society for medical oncology

ET Endocrine therapy

ER Estrogen receptors

FH	Family history
G	Gauge
H&E	Hematoxylin and eosin
HER2	Human epidermal growth factor receptor2
HR	Hormone receptors
IBC	Inflammatory BC
IBTR	Ipsilateral breast tumor recurrence
IHC	Immunohistochemistry
IKWG	International Ki67 in Breast Cancer Working Group
IM	Internal mammary
ISH	In-situ hybridization
LABC	Locally advanced breast cancer
LN	Lymph nodes
MDT	Multi-disciplinary team
Mets	Metastasis
MRI	Magnetic resonance imaging
MRM	Modified radical mastectomy.
NACT	Neoadjuvant chemotherapy
NCCN	National comprehensive cancer network
NMBC	Non metastatic breast cancer
NSM	Nipple-sparing mastectomy
OFS	Ovarian function suppression
pCR	Pathological complete response
PgR	Progesterone receptor
PO	Per oral
PST	**Primary systemic therapy**
QoL	**Quality of Life**

RT Radiotherapy

SC Supraclavicular

SLNB Sentinel LN biopsy

SNM Sono-mammography

SSM Skin-sparing mastectomy

TNBC Triple negative breast cancer

TCH Taxotere carboplatin Herceptin

U/S Ultrasound

WLE Wide local excision.

➢ Glossary

Menopausal status (Defined by NCCN)

Postmenopausal status:

- Permanent cessation of menses includes a profound and permanent decrease in ovarian estrogen synthesis.

Premenopausal status:

- It is the ongoing process of menses and normal ovarian estrogen synthesis.

Perimenopausal status:

- It is the transition status between the pre- and post-menopausal status with irregularities in menses and estrogen levels.

Definitions of molecular subtypes of breast cancer according to: (The ESMO Clinical Practice Guidelines, 2023):

- **Luminal A:** (ER-positive, HER2-negative, Ki67 low, PgR high)

- **Luminal B:**
  (HER2-negative subtype): (ER-positive, HER2-negative, and either, Ki67 high or PgR low)
  (HER2-positive subtype): (ER-positive, HER2-positive, any Ki67, any PgR)
- **HER2 overexpression (nonluminal):** (HER2-positive, ER and PgR absent)
- **Triple-negative:** (ER and PgR absent, HER2-negative)

Cancers with 1%–100% ER IHC staining are considered ER-positive.
Cancers with 1%–10% ER IHC staining are considered ER-low-positive.
HER2 positive patients (IHC+++ or ISH positive for gene amplification (HER2/CEP17 ratio ≥2.0 AND average HER2 copy number ≥ 4.0 signals/cell))

Ki67 index of 5% or less, or 30% or more, can be used to estimate prognosis for T1-2, N0-1 patients as per the International Ki67 in Breast Cancer Working Group (IKWG)

Definition of High-risk patients:
-HER2-positive disease
-TNBC
- ≥ cT2 or ≥ cN1
-Large primary tumor relative to breast size

- **Executive Summary**

This guidance provides an evidence-based approach to the diagnosis, staging, treatment and follow up of patients diagnosed with advanced breast cancer

Recommendations	***Strength of the recommendation***
Diagnosis, pathology and molecular biology	
At first diagnosis of MBC, a biopsy should be carried out to confirm histology and assess/re-assess tumour biology including ER, PgR, HER2 status & KI 67.	**Strong**
Staging and risk assessment	
The minimum imaging work-up for staging includes computed tomography (CT) of the chest and abdomen, and bone scintigraphy.	**Strong**
18F-FDG-PET)/CT may be used instead of CT and bone scans only as problem solving tool.	**Conditional**
The interval between imaging and starting treatment should be ≤4 weeks.	**Good practice statement.**
Evaluation of response should generally occur every 2-4 months depending on disease dynamics, location, extent of metastasis and type of treatment.	**Good practice statement.**
Disease monitoring intervals should not be shortened as there is no evidence of an OS benefit but potential for emotional and financial harm. Less frequent monitoring is acceptable, particularly for indolent disease.	**Good practice statement.**
If progression is suspected, additional tests should be carried out in a timely manner irrespective of planned intervals.	**Good practice statement.**
Repeat bone scans are a mainstay of evaluation for bone-only/predominant metastases, but image interpretation may be confounded by a possible flare	**Conditional**

during the first few months of treatment. MRI may be added to define response in specific locations.	
Impending fracture risk should be evaluated by CT or X-rays. In the case of suspected cord compression, MRI is the modality of choice.	**Strong**
Symptomatic patients should always undergo brain imaging, preferably with MRI.	**Strong**
HR-positive, HER2-negative breast cancer **First Line.**	
A CDK4/6 inhibitor combined with endocrine therapy (ET) may be used as first-line therapy for patients with ER-positive, HER2-negative MBC. However this depends on the availability, access-ability, patient comorbidity, and budget impact.	**Conditional**
Pre- and perimenopausal women should be offered OFS or ovarian ablation in addition to all endocrine-based therapies.	**Strong**
Second-line treatment.	
Selection of second-line therapy (chemotherapy versus further endocrine-based therapy) should be based on disease aggressiveness, extent and organ function, and consideration of the associated toxicity profile.	**Good practice statement.**
Everolimus- exemestane is a recommended option.	**Strong**
Tamoxifen or fulvestrant can also be combined with everolimus and is recommended. If everolimus is used, stomatitis prophylaxis must be used.	**Strong**
At least two lines of endocrine-based therapy are preferred before moving to chemotherapy in the absence of endocrine refractory disease and/or imminent organ failure.	**Strong**
In patients with imminent organ failure, chemotherapy is the preferred option.	**Strong**
For patients with endocrine-sensitive tumours, continuation of ET with agents not previously received in the metastatic setting is recommended.	**Strong**
Beyond second-line treatment	
Patients with tumours that are endocrine resistant should be considered for chemotherapy.	**Strong**

Sequential single-agent chemotherapy is generally preferred over combination strategies. In patients where a rapid response is needed due to imminent organ failure, combination chemotherapy is preferred.	**Strong**
Available drugs for single-agent chemotherapy include anthracyclines, taxanes, capecitabine, vinorelbine, and platinums.	**Strong**
HER2-positive breast cancer	
Standard first-line treatment of HER2-positive MBC should be trastuzumab-docetaxel regardless of HR status.	**Strong**
Docetaxel should be given for at least six cycles, if tolerated, followed by maintenance trastuzumab until progression.	**Strong**
An alternative taxane (paclitaxel) can be substituted for docetaxel.	**Strong**
ET can be added to trastuzumab maintenance after completion of chemotherapy for HER2-positive, HR-positive .	**Strong**
If chemotherapy is contraindicated in patients with HER2-positive, HR-negative MBC, HER2-targeted therapy without chemotherapy (e.g. trastuzumab) is recommended.	**Strong**
if taxane chemotherapy is contraindicated, a less toxic chemotherapy partner (e.g. capecitabine or vinorelbine) should be considered.	**Strong**
In selected cases of HER2-positive, HR-positive MBC where the patient is not suitable for first-line chemotherapy, ET (e.g. an AI) in combination with an HER2-targeted therapy, such as trastuzumab, or lapatinib, can be recommended.	**Strong**
The use of single-agent ET without HER2-targeted therapy in HER2-positive, HR-positive MBC is not routinely recommended unless comorbidities (e.g. cardiac disease) preclude the safe use of HER2-directed therapies.	**Conditional**
Patients with metastatic recurrence within 12 months of receiving adjuvant trastuzumab should follow the second-line therapy recommendations.	**Strong**
In later lines of therapy, lapatinib is an evidence-based therapy option to be used preferably in combinations (e.g. with capecitabine, trastuzumab or ET).	**Conditional**

TNBC	
In cases of imminent organ failure, combination therapy is preferred based on a taxane and/or anthracycline combination.	
After progression, all chemotherapy recommendations for HER2-negative disease also apply for TNBC, e.g. capecitabine, and vinorelbine.	
Site-specific management **Primary stage IV disease**	
For patients with newly diagnosed stage IV breast cancer and an intact primary tumour, therapeutic decisions should ideally be discussed in a multidisciplinary context.	**Good practice statement.**
Locoregional treatment of the primary tumour in the absence of symptomatic local disease does not lead to an OS benefit and is not routinely recommended.	**Good practice statement.**
In patients with local symptoms caused by the primary tumour or metastatic disease, the use of local treatment modalities should be evaluated.	**Strong**
Surgery of the primary tumour is recommended for patients who may benefit from salvage surgery (e.g. those with bone-only metastases, a good response to initial systemic therapy, HR-positive tumours, HER2-negative tumours, age <55 years and those with OMD).	**Strong**
Surgery or RT of the primary tumour should be carefully considered for circumstances in which they provide added value for symptom palliation or prevention of complications.	**Conditional**
Oligometastatic disease	
A multidisciplinary approach is essential to manage patients with bone metastases and prevent skeletal-related events (SREs).	**Good practice statement.**
Patients with OMD should be discussed in a multidisciplinary context to individualise management.	**Good practice statement.**
Multimodality treatment approaches involving locoregional therapy [e.g. high conformal radiotherapy (RT), image-guided ablation,selective internal RT and/or surgery] combined with systemic treatments are recommended, and should be tailored to the disease presentation in the individual patient.	**Strong**

Local ablative therapy to all metastatic lesions may be offered on an individual basis after discussion in a multidisciplinary setting.	**Conditional**
Bone metastases and bone-modifying agents	
A multidisciplinary approach is essential to manage patients with bone metastases and prevent skeletal-related events (SREs).	**Strong**
An orthopaedic evaluation is advised in the case of significant lesions in the long bones or vertebrae as well as in patients with MSCC to discuss the possible role of surgery.	**Strong**
RT is recommended for lesions at moderate risk of fracture and those associated with moderate to severe pain.	**Strong**
A single 8-Gy RT fraction is as effective as fractionated schemes in patients with uncomplicated bone metastases.	**Strong**
RT should be delivered after surgery for stabilisation or separation surgery for MSCC.	**Strong**
Bone-modifying agents (BMAs) are recommended for patients with bone metastases,regardless of symptoms.	**Strong**
Before the initiation of BMAs, patients should have a complete dental evaluation and ideally complete any required dental treatment. Calcium and vitamin D supplements should be prescribed.	**Strong**
The optimal duration of BMA therapy has not been defined but it is reasonable to interrupt therapy after 2 years for patients in remission.	**Good Practice Statement**
The ideal sequence of therapies has not been defined but it seems reasonable to document tumour response with a systemic treatment before suggesting locoregional therapy.	**Conditional**
Brain metastases and leptomeningeal metastases	
Brain metastases should be managed according to the recommendations outlined in the European Association of Neuro-Oncology-ESMO (EANO-ESMO) Clinical Practice Guideline (CPG) for the management of patients with brain metastases from solid tumours.	**Strong**
Leptomeningeal metastases should be treated according to the recommendations outlined in the EANO-ESMO CPG for the management of patients with leptomeningeal metastases from solid tumours.	**Strong**
Long-term implications and survivorship	

An interdisciplinary approach is critical, including specialised oncology and/or breast care nurses to proactively screen for and manage treatment-emergent toxicities.	**Good practice statement.**
Patients should be informed about treatment choices and side-effect profiles of recommended systemic treatments.	**Good practice statement.**
All treatments should include formal patient education regarding side-effects of management.	**Strong**
All efforts should be done to encourage integrated electronic medical records (EMR) in different hospitals.	**Strong**
QoL assessments should be incorporated into the evaluation of treatment efficacy.	**Strong**
Dose reduction and delay are effective strategies to manage toxicity in advanced disease.	**Strong**

➢ Introduction

Breast cancer is the most common cancer in females and the second most common in the Egyptian population with more than 26 thousand newly diagnosed cases(1). Moreover, it is also the second cause of cancer death in Egypt after hepatocellular carcinoma with estimated mortality rate around 10% in 2022. Approximately 46,000 incident cases are forecasted in 2050.

➢ Purpose and scope

These guidelines will help to improve the quality of care for advanced breast cancer patients via providing a uniform standard of care across the country to help in early diagnosis and treatment for breast cancer, with less aggressive treatment options and improved clinical outcomes. These guidelines cover primary diagnosis, staging, treatment and follow-up of advanced breast cancer patients.

➢ Target audience

Clinicians who are involved in the care and treatment of patients with breast cancer, including medical oncologists, radiation oncologists, clinical oncologists , surgeons, interventional radiologists, radiologists and pathologists.

➢ Methodology

A comprehensive search for guidelines was undertaken to identify the most relevant guidelines to consider for adaptation. inclusion/exclusion criteria followed in the search and retrieval of guidelines to be adapted:

- Selecting only evidence-based guidelines (guidelines must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence). - Selecting only national and/or international guidelines.
- Specific range of dates for publication (using Guidelines published or updated 2015 and later).
- Selecting peer reviewed publications only.
- Selecting guidelines written in English language.
- Excluding guidelines written by a single author not on behalf of an organization to be valid and comprehensive, a guideline ideally requires multidisciplinary input.
- Excluding guidelines published without references as the panel needs to know whether a thorough literature review was conducted and whether current evidence was used in the preparation of the recommendations.

All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least two members. the panel decided a cutoff point or rank the guidelines (any guideline scoring above 50% on the rigor dimension was retained)

The NCCN, ESMO, NICE guidelines are the main sources used while formulating the national guidelines for breast cancer.

➢ Evidence assessment

According to WHO handbook for Guidelines we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent recommendations. Detailed information on GRADE is available through the on the following sites:

. GRADE working group: http://www.gradeworkingroup.org

. GRADE online training modules: http://cebgrade.mcmaster.ca/

. GRADE profile software: http://ims.cochrane.org/revman/gradepro

Table 1: Quality of evidence in GRADE

Quality level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Table 2: Significance of the four levels of evidence

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Table 3: Factors that determine how to upgrade or downgrade the quality of evidence.

Downgrade in presence of	Upgrade in presence of
Study limitations -1 Serious limitations -2 Very serious limitations	Dose-response gradient +1 Evidence of a dose-response gradient
Consistency -1 Important inconsistency	Direction of plausible bias +1 All plausible confounders would have reduced the effect
Directness -1 Some uncertainty -2 Major uncertainty	Magnitude of the effect +1 Strong, no plausible confounders, consistent and direct evidence
Precision -1 Imprecise data	+2 Very strong, no major threats to validity and direct evidence
Reporting bias -1 High probability of reporting bias	

➢ The strength of the recommendation

The strength of a recommendation communicates the importance of adherence to the recommendation:

Strong recommendations: With strong recommendations, the guideline communicates the message that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted as policy.

Conditional recommendations: These are made when there is greater uncertainty about the four factors above (Table 2) or if local adaptation must account for a greater variety in values and preferences, or when resource use makes the intervention suitable for some, but not for other locations. This means that there is a need for substantial debate and involvement of stakeholders before this recommendation can be adopted as policy.

When not to make recommendations; when there is lack of evidence on the effectiveness of an intervention, it may be appropriate not to make a recommendation.

➢ Recommendations

Diagnosis, pathology and molecular biology

- At first diagnosis of MBC, a biopsy should be carried out to confirm histology and assess/re-assess tumour biology including ER, PgR, HER2 status & KI 67.

Strong recommendation, high grade evidence (1).

Staging and risk assessment

- The minimum imaging work-up for staging includes computed tomography (CT) of the chest and abdomen, and bone scintigraphy.

Strong recommendation, high grade evidence (2,3).

- 18F-FDG-PET)/CT may be used instead of CT and bone scans only as problem solving tool.

Conditional recommendation, high grade evidence (2,3).

- The interval between imaging and starting treatment should be ≤4 weeks.

Good practice statement.

- Evaluation of response should generally occur every 2-4 months depending on disease dynamics, location, extent of metastasis and type of treatment.

Good practice statement.

- Disease monitoring intervals should not be shortened as there is no evidence of an OS benefit but potential for emotional and financial harm. Less frequent monitoring is acceptable, particularly for indolent disease.

Good practice statement.

- If progression is suspected, additional tests should be carried out in a timely manner irrespective of planned intervals.

Good practice statement.

- Repeat bone scans are a mainstay of evaluation for bone-only/predominant metastases, but image interpretation may be confounded by a possible flare during the first few months of treatment. MRI may be added to define response in specific locations.

Conditional recommendation, low grade evidence (3).

- Impending fracture risk should be evaluated by CT or X-rays. In the case of suspected cord compression, MRI is the modality of choice.

Strong recommendation, high grade evidence (4).

- Symptomatic patients should always undergo brain imaging, preferably with MRI.

Strong recommendation, high grade evidence (5).

HR-positive, HER2-negative breast cancer

- A CDK4/6 inhibitor combined with endocrine therapy (ET) may be used as first-line therapy for patients with ER-positive, HER2-negative MBC. However this depends on the availability, access-ability, patient comorbidity, and budget impact.

Conditional recommendation, high grade evidence (6-8).

- Pre- and perimenopausal women should be offered OFS or ovarian ablation in addition to all endocrine-based therapies.

Strong recommendation, high grade evidence (9).

Second-line treatment

- Selection of second-line therapy (chemotherapy versus further endocrine-based therapy) should be based on disease aggressiveness, extent and organ function, and consideration of the associated toxicity profile.

Good practice statement.

- Everolimus- exemestane is a recommended option

Strong recommendation, high grade evidence(10-13).

- Tamoxifen or fulvestrant can also be combined with everolimus and is recommended. If everolimus is used, stomatitis prophylaxis must be used.

Strong recommendation, high grade evidence (10-13).

- At least two lines of endocrine-based therapy are preferred before moving to chemotherapy in the absence of endocrine refractory disease and/or imminent organ failure.

Strong recommendation, very low grade evidence (14).

- In patients with imminent organ failure, chemotherapy is the preferred option.

Strong recommendation, low grade evidence(14).

- For patients with endocrine-sensitive tumours, continuation of ET with agents not previously received in the metastatic setting is recommended.

Strong recommendation, low grade evidence (14).

Beyond second-line treatment

- Patients with tumours that are endocrine resistant should be considered for chemotherapy.

Strong recommendation, very low grade evidence (14).

- Sequential single-agent chemotherapy is generally preferred over combination strategies. In patients where a rapid response is needed due to imminent organ failure, combination chemotherapy is preferred.

Strong recommendation, high grade evidence (14).

- Available drugs for single-agent chemotherapy include anthracyclines, taxanes, capecitabine, vinorelbine,and platinums .

Strong recommendation, high grade evidence(14).

HER2-positive breast cancer

- Standard first-line treatment of HER2-positive MBC should be trastuzumab-docetaxel regardless of HR status.

Strong recommendation, high grade evidence (15,16).

- Docetaxel should be given for at least six cycles, if tolerated, followed by maintenance trastuzumab until progression.

Strong recommendation, high grade evidence(15,16).

- An alternative taxane (paclitaxel) can be substituted for docetaxel

Strong recommendation, high grade evidence(15,16).

- ET can be added to trastuzumab maintenance after completion of chemotherapy for HER2-positive, HR-positive .

Strong recommendation, high grade evidence (17).

- If chemotherapy is contraindicated in patients with HER2-positive, HR-negative MBC, HER2-targeted therapy without chemotherapy (e.g. trastuzumab) is recmmended.

Strong recommendation, low grade evidence (18).

- if taxane chemotherapy is contraindicated, a less toxic chemotherapy partner (e.g. capecitabine or vinorelbine) should be considered.

Strong recommendation, low grade evidence.

- In selected cases of HER2-positive, HR-positive MBC where the patient is not suitable for first-line chemotherapy, ET (e.g. an AI) in combination with an HER2-targeted therapy, such as trastuzumab, or lapatinib, is recommended.

Strong recommendation, high grade evidence (19,20).

- The use of single-agent ET without HER2-targeted therapy in HER2-positive, HR-positive MBC is not routinely recommended unless comorbidities (e.g. cardiac disease) preclude the safe use of HER2-directed therapies.

Conditional recommendation, low grade evidence (21).

- Patients with metastatic recurrence within 12 months of receiving adjuvant trastuzumab should follow the second-line therapy recommendations.

Strong recommendation, high grade evidence (22).

- In later lines of therapy, lapatinib is an evidence-based therapy option to be used preferably in combinations (e.g. with capecitabine, trastuzumab or ET).

Conditional recommendation, low grade evidence(23).

TNBC

- In cases of imminent organ failure, combination therapy is preferred based on a taxane and/or anthracycline combination.

Conditional recommendation, low grade evidence (14).

- After progression, all chemotherapy recommendations for HER2-negative disease also apply for TNBC, e.g. capecitabine, and vinorelbine.

Strong recommendation, low grade evidence (14).

Site-specific management

Primary stage IV disease

- For patients with newly diagnosed stage IV breast cancer and an intact primary tumour, therapeutic decisions should ideally be discussed in a multidisciplinary context.

Good practice statement.

- Locoregional treatment of the primary tumour in the absence of symptomatic local disease does not lead to an OS benefit and is not routinely recommended.

Good practice statement.

- In patients with local symptoms caused by the primary tumour or metastatic disease, the use of local treatment modalities should be evaluated.

Strong recommendation, high grade evidence(24).

- Surgery of the primary tumour is recommended for patients who may benefit from salvage surgery (e.g. those with bone-only metastases, a good response to initial systemic therapy, HR-positive tumours, HER2-negative tumours, age <55 years and those with OMD).

Strong recommendation, high grade evidence(25).

- Surgery or RT of the primary tumour should be carefully considered for circumstances in which they provide added value for symptom palliation or prevention of complications.

Conditional recommendation, very low grade evidence(25).

Oligometastatic disease

- A multidisciplinary approach is essential to manage patients with bone metastases and prevent skeletal-related events (SREs).

Good practice statement.

- Patients with OMD should be discussed in a multidisciplinary context to individualise management.

Good practice statement.

- Multimodality treatment approaches involving locoregional therapy [e.g. high conformal radiotherapy (RT), image-guided ablation,selective internal RT and/or surgery] combined with systemic treatments are recommended, and should be tailored to the disease presentation in the individual patient.

Strong recommendation, very low grade evidence (26).

- Local ablative therapy to all metastatic lesions may be offered on an individual basis after discussion in a multidisciplinary setting.

Conditional recommendation, moderate grade evidence (26).

Bone metastases and bone-modifying agents

- A multidisciplinary approach is essential to manage patients with bone metastases and prevent skeletal-related events (SREs).

Strong recommendation, very low grade evidence (26).

- An orthopaedic evaluation is advised in the case of significant lesions in the long bones or vertebrae as well as in patients with MSCC to discuss the possible role of surgery.

Strong recommendation, very low grade evidence (26).

- RT is recommended for lesions at moderate risk of fracture and those associated with moderate to severe pain.

Strong recommendation, very low grade evidence (26).

- A single 8-Gy RT fraction is as effective as fractionated schemes in patients with uncomplicated bone metastases.

Strong recommendation, high grade evidence (26).

- RT should be delivered after surgery for stabilisation or separation surgery for MSCC.

Strong recommendation, low grade evidence(26).

- Bone-modifying agents (BMAs) are recommended for patients with bone metastases,regardless of symptoms.

Strong recommendation, high grade evidence (26).

- Before the initiation of BMAs, patients should have a complete dental evaluation and ideally complete any required dental treatment. Calcium and vitamin D supplements should be prescribed.

Strong recommendation, low grade evidence (26).

- The optimal duration of BMA therapy has not been defined but it is reasonable to interrupt therapy after 2 years for patients in remission.

Good Practice Statement

- The ideal sequence of therapies has not been defined but it seems reasonable to document tumour response with a systemic treatment before suggesting locoregional therapy.

Conditional recommendation, very low grade evidence(26).

Brain metastases and leptomeningeal metastases

- Brain metastases should be managed according to the recommendations outlined in the European Association of Neuro-Oncology-ESMO (EANO-ESMO) Clinical Practice Guideline (CPG) for the management of patients with brain metastases from solid tumours.

Strong recommendation, high grade evidence (27).

- Leptomeningeal metastases should be treated according to the recommendations outlined in the EANO-ESMO CPG for the management of patients with leptomeningeal metastases from solid tumours.

Strong recommendation, high grade evidence (27).

Long-term implications and survivorship

- An interdisciplinary approach is critical, including specialised oncology and/or breast care nurses to proactively screen for and manage treatment-emergent toxicities.

Good practice statement.

- Patients should be informed about treatment choices and side-effect profiles of recommended systemic treatments.

Good practice statement.

- All treatments should include formal patient education regarding side-effects of management.

Strong recommendation, high grade evidence (28).

- All efforts should be done to encourage integrated electronic medical records (EMR) in different hospitals

Strong recommendation, high grade evidence(28).

- QoL assessments should be incorporated into the evaluation of treatment efficacy.

Strong recommendation, high grade evidence(28).

- Dose reduction and delay are effective strategies to manage toxicity in advanced disease.

Strong recommendation, high grade evidence(28).

➢ Research Gaps

- Head-to-Head comparison for adjuvant Olaparib versus Capecitabine in TNBC received neoadjuvant treatment with residual disease.
- Pembrolizumab neoadjuvant exclusively versus neoadjuvant and adjuvant regarding survival benefit, toxicity including financial toxicity and quality of life.
- This guideline will be updated whenever there is new evidence.
- Randomized trials to determine the risks and benefits of brain screening in TNBC needed.

➢ Update of this guidline

This guideline will be updated whenever there is new evidence.

➢ Annexes

Annex 1.

American Joint Committee on Cancer (AJCC) TNM Staging System For Breast Cancer

Table 1. **Definitions for T, N, M**

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)*	Ductal carcinoma *in situ*
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension (round any measurement >1.0–1.9 mm to 2 mm)
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma

*Note: Lobular carcinoma *in situ* (LCIS) is a benign entity and is removed from TNM staging in the AJCC Cancer Staging Manual, 8th Edition.

Regional Lymph Nodes (N)

Clinical (cN)

cNX*	Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
cN1mi**	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; *or* in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; *or* in ipsilateral internal mammary lymph node(s) with level I, II axillary lymph node metastases; *or* metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Pathologic (pN)

pNX	Regional lymph nodes cannot be assessed (e.g., not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cells clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined.
pN2	Metastases in 4–9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes

Pathologic (pN)

pN3	Metastases in 10 or more axillary lymph nodes; *or* in infraclavicular (level III axillary) lymph nodes; *or* positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive level I, II axillary lymph nodes; *or* in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; *or* in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); *or* metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging); *or* pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or FNA/core needle biopsy respectively, with NO further resection of nodes

Distant Metastasis (M)

M0	No clinical or radiographic evidence of distant metastases*
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
cM1	Distant metastases detected by clinical and radiographic means
pM1	Any histologically proven metastases in distant organs; or if in non-regional nodes, metastases greater than 0.2 mm

Table 2. **AJCC Anatomic Stage Groups**

The Anatomic Stage Group table should only be used in global regions where biomarker tests are not routinely available.
Cancer registries in the U.S. must use the Clinical and Pathological Prognostic Stage Group tables for case reporting.

Stage 0	Tis	N0	M0	**Stage IIIA**	T0	N2	M0
Stage IA	T1	N0	M0		T1	N2	M0
Stage IB	T0	N1mi	M0		T2	N2	M0
	T1	N1mi	M0		T3	N1	M0
Stage IIA	T0	N1	M0		T3	N2	M0
	T1	N1	M0	**Stage IIIB**	T4	N0	M0
	T2	N0	M0		T4	N1	M0
Stage IIB	T2	N1	M0		T4	N2	M0
	T3	N0	M0	**Stage IIIC**	Any T	N3	M0
Notes:				**Stage IV**	Any T	Any N	M1

1. T1 includes T1mi.
2. T0 and T1 tumors with nodal micrometastases (N1mi) are staged as Stage IB.
3. T2, T3, and T4 tumors with nodal micrometastases (N1mi) are staged using the N1 category.
4. M0 includes M0(i+)
5. The designation pM0 is not valid; any M0 is clinical.
6. If a patient presents with M1 disease prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
7. Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided the studies are performed within 4 months of diagnosis in the absence of disease progression, and provided the patient has not received neoadjuvant therapy.
8. Staging following neoadjuvant therapy is designated with "yc" or "yp" prefix to the T and N classification. There is no anatomic stage group assigned if there is a complete pathological response (pCR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

The AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing

Annex 2.

Spine instability neoplastic score (SINS)

SINS component	Score
Location	
Junctional (occiput–C2, C7–T2, T11–L1, L5–S1)	3
Mobile spine (C3–6, L2–4)	2
Semirigid (T3–10)	1
Rigid (S2–5)	0
Pain*	
Yes	3
Occasional pain but not mechanical	2
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
>50% collapse	3
<50% collapse	2
No collapse with >50% body involved	1
None of the above	0
Posterolateral involvement of the spinal elementsy†	
Bilateral	3
Unilateral	1
None of the above	0

Criteria of instability. Total score (TS) 0–6 : stable spine, TS 7–12 : potential unstable spine, TS 13–18 : unstable spine. Recommendation : TS ≥7, consider surgical intervention. *Pain improvement with recumbency and/or pain with movement/loading of the spine, †Facet, pedicle, or costovertebral joint fracture or replacement with tumor

Ho-Young Park et.al., J Korean Neurosurg Soc 57 (2) : 100-107, 2015

➢ References

1. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021;32(12):1475-1495

2. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649.
3. Lee CI, Gold LS, Nelson HD, et al. Comparative effectiveness of imaging modalities to determine metastatic breast cancer treatment response. Breast. 2015;24(1):3-11.
4. Fourney DR, Frangou EM, Ryken TC, et al. Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. J Clin Oncol. 2011;29(22):3072-3077.
5. Komorowski AS, Warner E, MacKay HJ, et al. Incidence of brain me- tastases in nonmetastatic and metastatic breast cancer: is there a role for screening? Clin Breast Cancer. 2020;20(1):e54-e64.
6. Cristofanilli M, Rugo HS, Im SA, Slamon DJ, Harbeck N, Bondarenko I, Masuda N et al. Overall Survival with Palbociclib and Fulvestrant in Women with HR+/HER2- ABC: Updated Exploratory Analyses of PALOMA-3, a Double-blind, Phase III Randomized Study.Clin Cancer Res. 2022 Aug 15;28(16):3433-3442. doi: 10.1158/1078-0432.CCR-22-0305.
7. Goetz MP, Toi M, Huober J, Sohn J, Trédan O, Park IH et al. Abemaciclib plus a nonsteroidal aromatase inhibitor as initial therapy for HR+, HER2- advanced breast cancer: final overall survival results of MONARCH 3., Ann Oncol. 2024 Aug;35(8):718-727.
8. Ribociclib plus Endocrine Therapy in Early Breast Cancer.Slamon D, Lipatov O, Nowecki Z, McAndrew N, Kukielka-Budny B, Stroyakovskiy et al. N Engl J Med. 2024 Mar 21;390(12):1080-1091.
9. Klijn JG, Beex LV, Mauriac L, et al. Combined treatment with buserelin and tamoxifen in premenopausal metastatic breast cancer: a ran- domized study. J Natl Cancer Inst. 2000;92(11):903-911.
10. Baselga J, Campone M, Piccart M, et al. Everolimus in post- menopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012;366(6):520-529.
11. Cook MM, Al Rabadi L, Kaempf AJ, et al. Everolimus plus exemestane treatment in patients with metastatic hormone receptor-positive breast cancer previously treated with CDK4/6 inhibitor therapy. Oncologist. 2021;26(2):101-106.
12. Jerusalem G, de Boer RH, Hurvitz S, et al. Everolimus plus exemestane vs everolimus or capecitabine monotherapy for estrogen receptor- positive, HER2-negative advanced breast cancer: the BOLERO-6 ran- domized clinical trial. JAMA Oncol. 2018;4(10):1367-1374.
13. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. Ann Oncol. 2014;25(12):2357-2362.
14. Im SA, Gennari A ,Park YH, Kim JH et al., Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, staging and treatment of patients with metastatic breast cancer, Ann. Oncol, 8,(3): 1-24, 2023
15. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anas- trozole versus anastrozole alone for the treatment of post- menopausal women with human epidermal growth factor receptor 2- positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol. 2009;27(33):5529-5537.
16. Yuan Z, Huang J-J, Hua X, et al. Trastuzumab plus endocrine therapy or chemotherapy as first-line treatment for metastatic breast cancer with hormone receptor-positive and HER2-positive: the SYSUCC-002 randomized clinical trial. J Clin Oncol. 2021;39(suppl 15):1003.

17. Rimawi M, Ferrero JM, de la Haba-Rodriguez J, et al. First-line tras- tuzumab plus an aromatase inhibitor, with or without pertuzumab, in human epidermal growth factor receptor 2-positive and hormone receptor-positive metastatic or locally advanced breast cancer (PERTAIN): a randomized, open-label phase II trial. J Clin Oncol. 2018;36(28):2826-2835.
18. Cortés J, Fumoleau P, Bianchi GV, et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced hu- man epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2012;30(14):1594-1600
19. Johnston SRD, Hegg R, Im SA, et al. Phase III, randomized study of dual human epidermal growth factor receptor 2 (HER2) blockade with lapatinib plus trastuzumab in combination with an aromatase inhib- itor in postmenopausal women with HER2-positive, hormone receptor-positive metastatic breast cancer: ALTERNATIVE. J Clin Oncol. 2018;36(8):741-748.
20. Johnston S, Pippen J Jr, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for post- menopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol. 2009;27(33):5538-5546.
21. https://www.cancer.org/cancer/types/breast-cancer/treatment/treatment-of-breast-cancer-by-stage/treatment-of-stage-iv-advanced-breast-cancer.html#:~:text=HER2%2Dpositive%20cancers,An%20antibody%2Ddrug%20conjugate
22. Bartsch R, Cameron D, Ciruelos E, Criscitiello C, Curigliano G, Duhoux FP, Foukakis T, Gligorov J, Harbeck N, LeVasseur N, Okines A, Penault-Llorca F, Müller V.Expert recommendations on treatment sequencing and challenging clinical scenarios in human epidermal growth factor receptor 2-positive (HER2-positive) metastatic breast cancer.Cancer Treat Rev. 2025 Jan;132:102853.
23. ASCO Educational Book: 2022,https://ascopubs.org/doi/pdf/10.1200/EDBK_351222#:~:text=In%20later%20lines%20of%20therapy,in%20the%20late%2Dline%20scenario.
24. Ryckman JM, Thomas TV, Wang M, Wu X, Siva S, Spratt DE, Slotman B, Pal S, Chapin BF, Fitzal F, Soran A, Bex A, Louie AV, Lehrer EJ, Zaorsky NG., Local Treatment of the Primary Tumor for Patients With Metastatic Cancer (PRIME-TX): A Meta-Analysis.
Int J Radiat Oncol Biol Phys. 2022 Dec 1;114(5):919-935.
25. Demirors B, Goktepe B, Medeck H, Ozbas S, Soran A, et al., The Role of Primary Surgery in De Novo Metastatic Breast Carcinoma.Eur J Breast Health. 2023 Apr 1;19(2):110-114.
26. Gennari A, André F, Barrios C H et al., ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer, 32,12:1475-1495.
27. Le Rhun E, Guckenberger M, Smits M, et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol. 2021;32(11): 1332-1347.
28. John Sieh Dumbuya,Bashir Ahmad, Cizheng Zeng, Xiuling Chen & Jun Lu, Assessing the effectiveness of measurement scales in evaluating the health-related quality of life in rare disease patients after treatment: a systematic review Health and Quality of Life Outcomes, 22,108 (2024).