



ESMO POCKET GUIDELINES

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ESMO CLINICAL PRACTICE GUIDELINES

ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer

Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, Dent R, Fenlon D, Gligorov J, Hurvitz SA, Im S-A, Krug D, Kunz WG, Loi S, Penault-Llorca F, Rike J, Robson M, Rugo HS, Saura C, Schmid P, Singer CF, Spanic T, Tolaney SM, Turner NC, Curigliano G, Loibl S, Paluch-Shimon S and Harbeck N, on behalf of the ESMO Guidelines Committee
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ESMO Metastatic Breast Cancer Living Guideline v1.1 (May 2023)

Curigliano G, Castelo-Branco L, Gennari A, Harbeck N, Criscitiello C and Trapani D, on behalf of the Clinical Practice Guideline author group
<https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline>

ESMO POCKET GUIDELINES (CONT'D)

Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes:

ESMO Clinical Practice Guideline

Sessa C, Balmaña J, Bober SL, Cardoso MJ, Colombo N, Curigliano G, Domchek SM, Evans DG, Fischerova D, Harbeck N, Kuhl C, Lemley B, Levy-Lahad E, Lambertini M, Ledermann JA, Loibl S, Phillips K-A and Paluch-Shimon S, on behalf of the ESMO Guidelines Committee
Ann Oncol 2023;34(1):33-47

[https://www.annalsofoncology.org/article/S0923-7534\(22\)04193-X/fulltext](https://www.annalsofoncology.org/article/S0923-7534(22)04193-X/fulltext)

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

Loibl S, André F, Bachelot T, Barrios CH, Bergh J, Burstein HJ, Cardoso LMJ, Carey LA, Dawood S, Del Mastro L, Denkert C, Fallenberg EM, Francis PA, Gamal-Eldin H, Gelmon K, Geyer CE, Gnant M, Guarneri V, Gupta S, Kim SB, Krug D, Martin M, Meattini I, Morrow M, Janni W, Paluch-Shimon S, Partridge A, Poortmans P, Puszta L, Regan MM, Sparano J, Spanio T, Swain S, Tjulandin S, Tof M, Trapani D, Tutt A, Xu B, Curigliano G and Harbeck N, on behalf of the ESMO Guidelines Committee

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ESMO GUIDE TO EVALUATION OF DATA

ESMO POCKET GUIDELINES PROVIDE YOU WITH A CONCISE SUMMARY OF THE FUNDAMENTAL RECOMMENDATIONS MADE IN THE PARENT GUIDELINES IN AN EASILY ACCESSIBLE FORMAT.

This quick reference booklet provides you with the most important content of the ESMO Clinical Practice Guidelines (CPGs) on the management of breast cancer (including metastatic breast cancer, hereditary breast cancer syndromes and early breast cancer). Key content includes diagnostic criteria, staging of disease, treatment plans and follow-up. The ESMO CPGs on breast cancer are intended to provide you with a set of recommendations for the best standards of care for breast cancer, using evidence-based medicine. Implementation of ESMO CPGs facilitates knowledge uptake and helps you to deliver an appropriate quality of focused care to your patients.

The approval and licensed indication of drugs mentioned in this pocket guideline may vary in different countries. Please consult your local prescribing information. This booklet can be used as a quick reference guide to access key content on evidence-based management of breast cancer.

Please visit <http://www.esmo.org> or <http://oncologypro.esmo.org> to view the full guidelines.

TABLE OF CONTENTS

9-28

METASTATIC BREAST CANCER

DIAGNOSIS	9
STAGING AND RISK ASSESSMENT.....	11
TREATMENT	12
Luminal breast cancer.....	12
HER2-positive breast cancer.....	15
Triple-negative breast cancer.....	19
Hereditary breast cancer.....	21
Site-specific management	22
New drugs	26
PERSONALISED MEDICINE.....	26
LONG-TERM IMPLICATIONS AND SURVIVORSHIP.....	26
Side-effects.....	26
Palliative care.....	27
Patient perspective.....	27

29-38

HEREDITARY BREAST CANCER SYNDROMES

INCIDENCE AND EPIDEMIOLOGY.....	29
POST-TEST COUNSELLING AND FOLLOW-UP OF INDIVIDUALS WITH HEREDITARY BREAST AND OVARIAN CANCER SYNDROME (HBOC).....	31
Genetic counselling	31
Follow-up.....	31
BREAST CANCER RISK MANAGEMENT	31
Screening for women with high-risk pathogenic variants	31
Lifestyle factors and breast cancer risk	34
Risk-reducing medication	35
Risk-reducing surgery.....	35
Approach to male carriers of high-risk pathogenic variants	35
Screening for additional malignancies	36
COUNSELLING, RISK-REDUCTION AND SCREENING IN THE PRESENCE OF OTHER MODERATE-HIGH RISK PATHOGENIC VARIANTS.....	36

TABLE OF CONTENTS (CONT'D)

REPRODUCTIVE AND ENDOCRINOLOGICAL ISSUES IN INDIVIDUALS WITH HBOC	37
Contraception	37
Fertility	37
Management of menopausal symptoms	37
UNIQUE PSYCHOLOGICAL ISSUES FOR INDIVIDUALS WITH HBOC	37
PERSONALISED MEDICINE AND FUTURE DIRECTIONS.....	38

39-63

EARLY BREAST CANCER (EBC)

SCREENING	39
DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY	39
STAGING AND RISK ASSESSMENT.....	43
MANAGEMENT OF EBC.....	48
General treatment principles.....	48
Patient communication and shared decision making.....	48
Locoregional treatment	48
Systemic treatment	52
Special situations	58
FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP	61
General follow-up considerations.....	61
Long-term implications	61
Reproductive and sexual health considerations.....	63
Psychosocial considerations	63

64-66

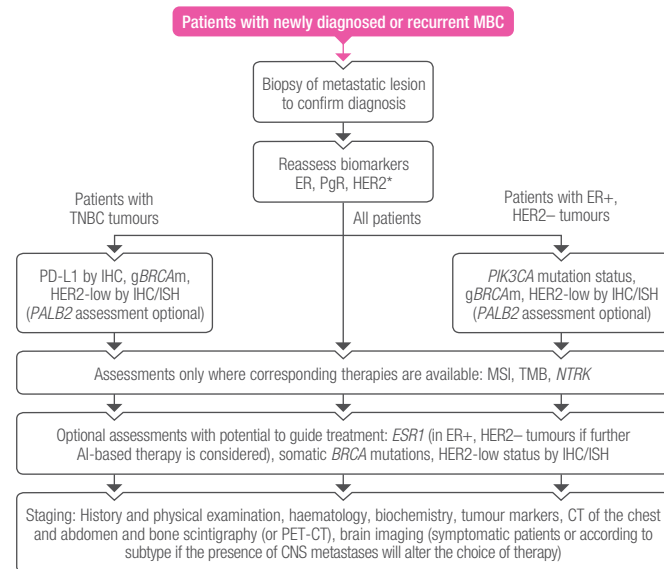
GLOSSARY

METASTATIC BREAST CANCER

DIAGNOSIS

- The recommended diagnostic work-up for metastatic breast cancer (MBC) is shown in the figure below

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; ISH, *in situ* hybridisation; 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 rebiopsy 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

STAGING AND RISK ASSESSMENT

- Imaging work-up for staging should include computed tomography (CT) of the chest/abdomen and bone scintigraphy
 - [¹⁸F]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
 - Patients with symptomatic disease should always undergo brain imaging, preferably with MRI

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

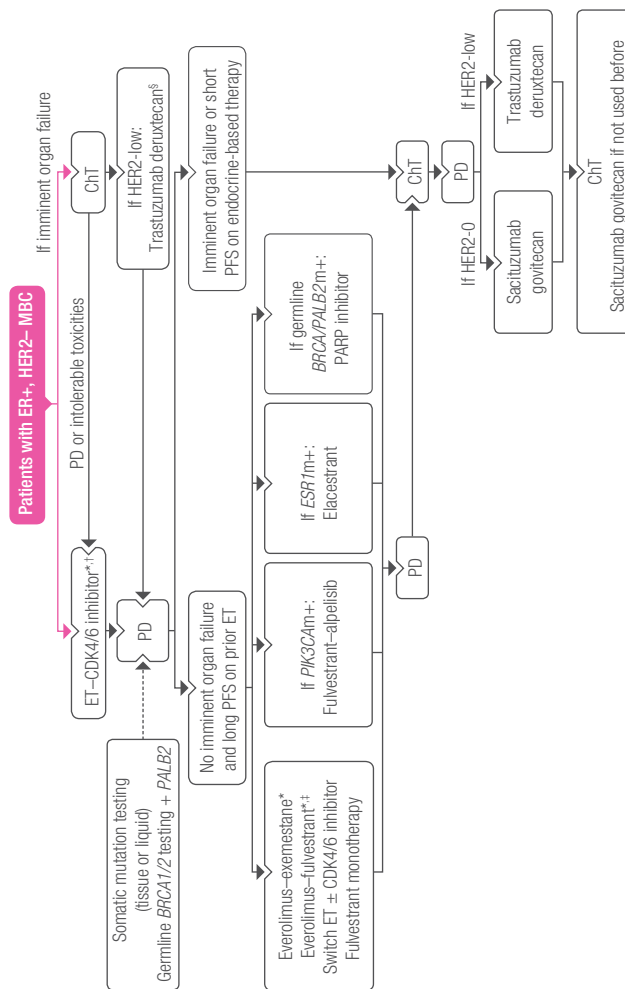
Luminal breast cancer

- Management options for ER-positive, HER2-negative MBC are shown in the figure on the next page
- Premenopausal women may be treated in the same way as postmenopausal women as long as 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
 - Relapse within 12 months of completing adjuvant ET
 - 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
 - An aromatase inhibitor (AI)–CDK4/6 inhibitor combination 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

MANAGEMENT OF ER-POSITIVE, HER2-NEGATIVE MBC



*OFS if the patient is premenopausal

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*

*Preferred if the patient is *ESR1* mutation positive

*Trastuzumab deruxtecan can also be given following adjuvant ChT in the setting of fast progression (DESTINY-Breast04/EMA indication)

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4 and 6; ChT, chemotherapy; EMA, European Medicines Agency; 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; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

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*-mutated tumours, prior exposure to an AI ($\pm$ CDK4/6 inhibitor) and appropriate glycated haemoglobin levels
 - Hyperglycaemia 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 with steroid mouthwash must be used during everolimus treatment
- Elacestrant (if available) is an option for patients with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer progressing after at least one line of ET
- 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

Beyond second line

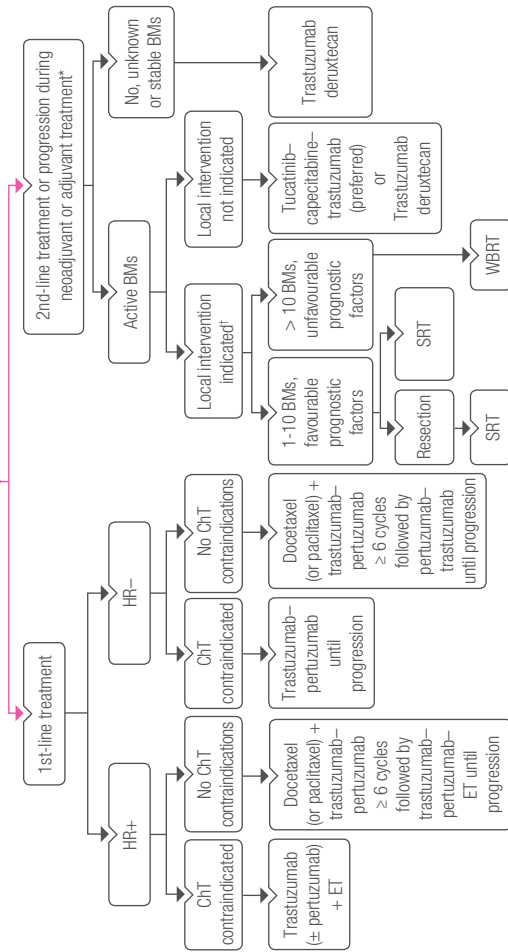
- Treatment decisions should consider sensitivity to previous treatments, time to progression, gBRCAm status, tumour biology and mechanisms of resistance that may have arisen during previous treatments
- For endocrine-sensitive tumours, continuation of ET with agents not previously received in the metastatic setting may be an option
- For endocrine-resistant tumours where targeted agents have already been used or ruled out due to lack of therapeutically-relevant molecular alterations, ChT should be considered
- Sequential single-agent ChT is generally preferred over combination strategies
 - Single-agent ChT options include anthracyclines, taxanes, capecitabine, eribulin, vinorelbine and platinum
 - The optimal ChT sequence in MBC has not been established
 - When a rapid response is needed due to imminent organ failure, combination ChT is preferred
- Rechallenge with anthracyclines or taxanes is feasible in patients with a DFI ≥ 12 months
 - Liposomal anthracyclines or protein-bound paclitaxel may be considered for the rechallenge, if available
 - Anthracycline lifetime cumulative dose limits must be considered; cardiac monitoring is mandatory
- Bevacizumab (if available) plus taxane or capecitabine is a first-line ChT option
- If capecitabine is used, patients should undergo germline variant testing for lack of the enzyme, dihydropyrimidine dehydrogenase, before treatment starts
- ChT should generally be continued until PD or intolerable toxicity, except for anthracyclines where the cumulative dose limit must be considered
- Sacituzumab govitecan should be considered for patients with HR-positive/HER2-0 MBC after at least two lines of ChT
- Trastuzumab deruxtecan should be considered for patients with HER2-low MBC after at least one line of ChT

HER2-positive breast cancer

First-line treatment

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

Patients with HER2+ MBC



*Including neoadjuvant dual blockade or adjuvant T-DM1

†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

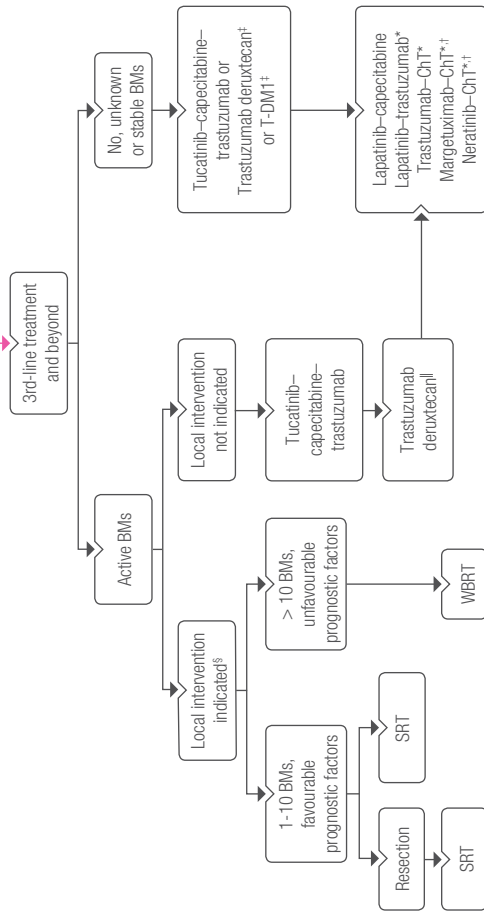
Second-line treatment

- 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 treatment and beyond

- Third- and further-line management options for HER2-positive MBC are shown in the figure on the next page
- The choice of third-line treatment depends on prior second-line therapy, patient characteristics, toxicity profiles and availability

Patients with HER2+ 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

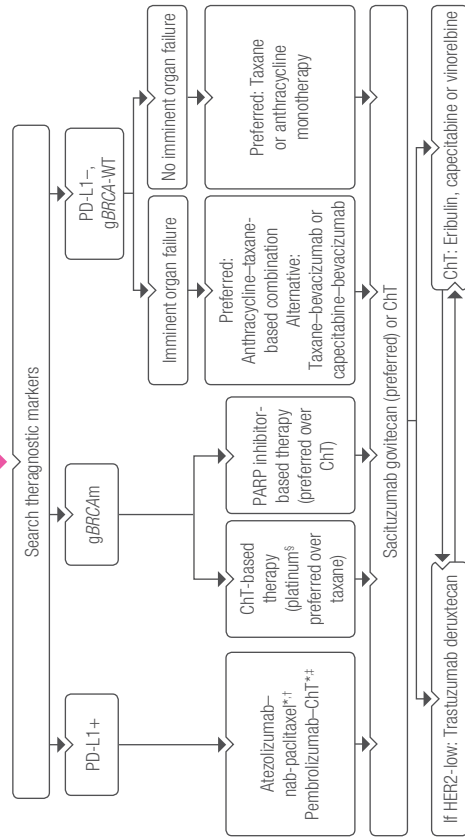
- The most active treatment options appear to be tucatinib–capecitabine–trastuzumab, trastuzumab deruxtecan and T-DM1
- In later lines of therapy, lapatinib is an evidence-based therapy option to be used preferably in combinations (e.g. with capecitabine, trastuzumab or ET)
- Neratinib and margetuximab can be considered for late-line treatment [both Food and Drug Administration (FDA) approved, not European Medicines Agency (EMA) approved]
 - 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, trastuzumab beyond progression should be considered

Triple-negative breast cancer

- Management options for metastatic TNBC (mTNBC) are shown in the figure on the next page

First-line treatment

- For PD-L1-positive tumours, the preferred option is ChT in combination with an immune checkpoint inhibitor (ICI)
 - In case of PD-L1 immune cell positivity, atezolizumab–nab-paclitaxel is an option for *de novo* MBC or when the DFI is ≥ 12 months (EMA approved, not FDA approved)
 - In case of combined positive score (CPS) ≥ 10 , pembrolizumab plus paclitaxel, nab-paclitaxel or carboplatin–gemcitabine can be considered in *de novo* advanced disease or when the DFI is ≥ 6 months
- For gBRCAm and PD-L1-negative disease, the preferred options are olaparib, talazoparib or carboplatin (see section on hereditary BC on pages 21 and 22)
- For gBRCA-wild type and PD-L1-negative disease, the initial treatment is ChT
 - The choice of ChT depends on previous treatments, disease presentation, DFI and patient considerations
 - Taxane monotherapy is the most frequently used option
 - Anthracyclines can be used in cases with no prior exposure or if rechallenge is possible
 - In case of imminent organ failure, combination therapy with a taxane and/or anthracycline with bevacizumab (first line only) is preferred



*May be considered as monotherapy in further lines in case of high PD-L1 positivity and no previous exposure to ICI

†EMA approved, not FDA approved

‡ICI physician's choice of nab-paclitaxel, paclitaxel or gemcitabine-carboplatin

§Not used previously

ChT: chemotherapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; gBRCA2m, germline *BRCA2* mutation; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; mTNBC, metastatic triple-negative breast cancer; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death-ligand 1; WT, wild type

Progression after anthracyclines and taxanes

- Sacituzumab govitecan is the preferred treatment option after prior ChT
- After progression on sacituzumab govitecan, all ChT recommendations for HER2-negative disease also apply for TNBC, such as eribulin, capecitabine and vinorelbine
- ICI monotherapy is not recommended in later lines
 - Pembrolizumab may be an option for patients with tumours strongly positive for PD-L1 if they have not received prior ICI therapy or do not have access to a clinical trial
- For patients with HER2-low MBC, trastuzumab deruxtecan should be considered after at least one line of ChT
- Antiandrogen therapy or inhibitors targeting PI3K or AKT are not recommended outside a clinical trial

Maintenance

- No Phase III study has specifically addressed the question of maintenance therapy in TNBC
- ICI maintenance is acceptable in patients who have received an initial ChT-ICI combination, in the absence of safety issues
- Bevacizumab maintenance may be used after an initial bevacizumab-taxane or bevacizumab-capecitabine combination

Hereditary breast cancer

- Patients with HER2-negative MBC and germline pathogenic (or likely pathogenic) variants in *BRCA1* or *BRCA2* should be offered a PARP inhibitor (olaparib or talazoparib) as an alternative to ChT, irrespective of HR status
 - Prior treatment with anthracyclines-taxanes is not required before offering PARP inhibitor treatment to patients with MBC and gBRCAm; nor should patients with HR-positive disease be required to demonstrate complete endocrine resistance
- Platinum-based ChT (single agent or combined with paclitaxel) is associated with a substantial progression-free survival (PFS) benefit in patients with MBC and gBRCAm
- There are no studies directly comparing PARP inhibitors with a platinum agent, but in pivotal trials, health-related quality of life (QoL) was better with PARP inhibitors
- There are no studies comparing PARP inhibitors with ET (alone or with targeted therapies) in patients with HR-positive disease

- The optimal sequencing of PARP inhibitors with other active treatments, such as ChT–ICI in mTNBC or ET–targeted therapy in HR-positive disease, is unknown
 - Sequencing decisions should be based on factors such as prior treatment response, disease burden, PD-L1 status, *PIK3CA* status, HR status and the relative toxicities of the different approaches
- When a PARP inhibitor is considered, patients should be offered genetic testing for pathogenic variants in *BRCA1* and *BRCA2* regardless of age, family history or BC subtype

Site-specific management

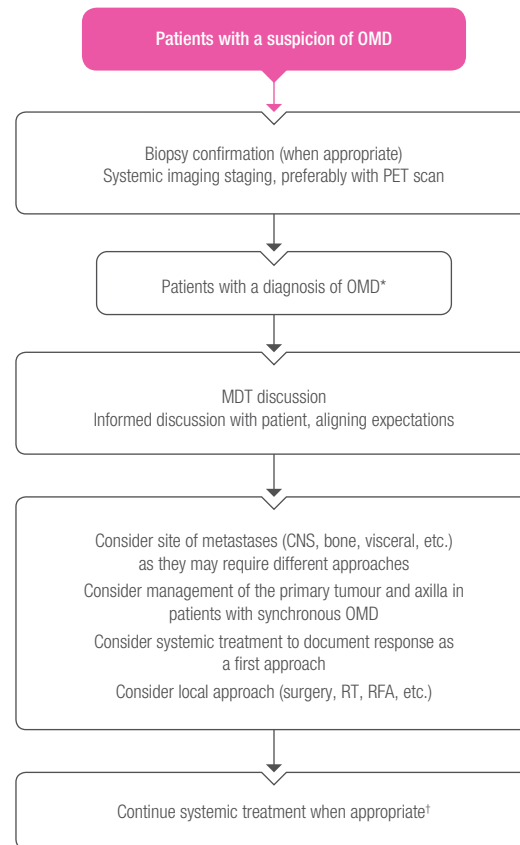
Primary stage IV disease

- For patients with newly diagnosed stage IV BC and an intact primary tumour, therapeutic decisions should ideally be discussed in a multidisciplinary context
- LRT of the primary tumour in the absence of symptomatic local disease does not lead to an OS benefit and is not routinely recommended
- In patients with local symptoms caused by the primary tumour or metastatic disease, the use of local treatment modalities should be evaluated
- Surgery of the primary tumour may be considered for patients with bone-only metastasis, HR-positive tumours, HER2-negative tumours, patients of < 55 years, patients with oligometastatic disease (OMD) and those with a good response to initial systemic therapy

OMD

- A proportion of patients with MBC may present or recur with limited metastatic disease, referred to as OMD
- The clinical challenge is whether treatment should follow a palliative approach or be escalated to pursue complete and sustained remission (curative approach)
- Management options for OMD are shown in the figure on the next page
- The dynamics in chronic metastatic conditions should be reviewed to identify induced or recurrent OMD
- A complete imaging history should be available for decisions on OMD care
- Patients with OMD should be discussed in a multidisciplinary context to individualise management
- Multimodality treatment approaches involving LRT [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 according to disease presentation in the individual patient

MANAGEMENT OF OMD



*Consider elements in current definitions, i.e. limited or low-volume metastatic disease; up to five lesions in total, not necessarily in the same organ; all potentially amenable to receive local treatment

†The duration of systemic treatment remains a topic of debate

CNS, central nervous system; MDT, multidisciplinary team; OMD, oligometastatic disease; PET, positron emission tomography; RFA, radiofrequency ablation; RT, radiotherapy

- Some subtypes of BC may be very sensitive to systemic treatment
 - The ideal therapy sequence has not been defined
 - It is reasonable to document tumour response with systemic treatment before suggesting localised RT or surgery
- Local ablative therapy to all metastatic lesions may be offered on an individual basis after discussion in a multidisciplinary setting

Bone metastases and bone-modifying agents

- A multidisciplinary approach is essential to manage patients with bone metastases and to prevent skeletal-related events (SREs)
- Appropriate diagnostic imaging (i.e. CT for fracture risk and MRI for suspected cord compression) is recommended to define the extent of disease and the risk of fractures
- An orthopaedic evaluation is advised in case of significant lesions in long bones or vertebrae, as well as in patients with metastatic spinal cord compression (MSCC) to discuss the possible role of surgery
- RT is recommended for lesions at moderate risk of fracture and those associated with moderate to severe pain
 - A single 8-Gy RT fraction is as effective as fractionated schemes in uncomplicated bone metastases
 - RT should be delivered after surgery for stabilisation or after separation surgery for MSCC
- Bone-modifying agents (BMAs; e.g. bisphosphonates or denosumab) are recommended for patients with bone metastases, regardless of symptoms
- Zoledronate can be administered every 12 weeks in patients with stable disease after 3-6 monthly treatments
- Denosumab should be administered every 4 weeks and is more effective than zoledronate in delaying first and subsequent SREs
- For patients progressing on a BMA, it is unclear if changing to another agent with a different mechanism of action is of benefit
 - In patients progressing on intravenous bisphosphonates, denosumab could be an alternative
- Before BMA initiation, patients should have a complete dental evaluation (and should ideally complete any required dental treatment) and calcium and vitamin D supplements should be prescribed
- The optimal duration of BMA therapy has not been defined but it is reasonable to interrupt therapy after 2 years for patients in remission

BMIs and leptomeningeal metastases

- BMs should be managed according to the recommendations outlined in the European Association of Neuro-Oncology (EANO)–ESMO Clinical Practice Guideline (CPG) for the management of patients with BMs from solid tumours (see: <https://www.esmo.org/guidelines/guidelines-by-topic/neuro-oncology/brain-metastasis-from-solid-tumours>)
- The presence of BMs should be explored by brain imaging in all patients who present with clinical signs or symptoms of raised intracranial pressure, seizures or new neurological deficits
- In mTNBC or HER2-positive MBC, brain imaging could be considered in asymptomatic patients, based on the high probability of BMs in these subtypes, if detection of CNS metastases will alter the choice of systemic therapy
- The diagnostic work-up of patients with suspected BMs should include cranial MRI
 - If MRI is not available, contrast CT can be used
- Patients with a single BM should be considered for surgery whenever possible; stereotactic radiosurgery (SRS) is recommended for patients with a limited number (1-4) of BMs
 - SRS may also be considered for patients with a higher number of BMs (4-10), provided the cumulative tumour volume is < 15 mL
- Whole brain RT (WBRT) should be considered in case of multiple BMs
- In HER2-positive MBC, anti-HER2 therapies may be considered in patients not requiring immediate local therapy
 - Tucatinib (together with trastuzumab and capecitabine) has demonstrated a significant OS improvement in patients with active BMs
 - The use of intrathecal trastuzumab remains investigational
- In patients with HER2-negative BC, ChT may be considered
- Leptomeningeal metastases (LMs) should be treated according to the recommendations outlined in the EANO–ESMO CPG for the management of patients with LMs from solid tumours (see: <https://www.esmo.org/guidelines/guidelines-by-topic/neuro-oncology/leptomeningeal-metastasis>)
- Methotrexate, cytarabine (including liposomal cytarabine) or thiopeta are commonly used for intrathecal treatment of LMs, but they have not demonstrated improvements in OS
- RT should be considered for patients with symptomatic LMs, either as localised RT for nodular lesions or as WBRT for extensive nodular or linear LMs

New drugs

- Despite progress in treating MBC, the disease remains incurable and effective treatment options are limited for some patient populations
- Several antibody–drug conjugates, utilising antibodies, linkers and chemotherapeutics, have entered the clinical trial pipeline for a variety of BC subtypes and eligible patients should be encouraged to participate in these trials

PERSONALISED MEDICINE

- Standard therapies for MBC are personalised based on biomarkers
- In addition, there are now several tissue and site-agnostic approvals. For example:
 - Larotrectinib and entrectinib are approved for patients with solid tumours expressing an *NTRK* gene fusion
 - Pembrolizumab is FDA approved for patients with unresectable or metastatic MSI-high/mismatch repair deficient solid tumours who have PD and no alternative treatment options [EMA approval in this setting is not tumour agnostic but is for specific tumour types (excludes BC)]
 - These biomarkers should be tested once subtype-specific standard therapies have been exhausted
- New drugs are being evaluated that have documented activity across several MBC subtypes, and may require assessment of new biomarkers (e.g. human epidermal growth factor receptor 3) once therapeutic efficacy and biomarker validation have been completed

LONG-TERM IMPLICATIONS AND SURVIVORSHIP

- In MBC, regular evaluation of disease status and therapy-related toxicities should include clinical assessments, blood tests, imaging and patient-reported outcomes (PROs)

Side-effects

- The most common side-effect of BC treatment is fatigue, which can appear early in treatment, be overwhelming and is not eased by rest
 - Contributing factors should be considered, including concomitant medications, anaemia and PD
 - Recommended management includes dose reduction of current treatment and physical activity with intermittent rest periods
- Nausea and vomiting are common side-effects of many therapies and may be managed using both prophylaxis and rescue medications
- Bone marrow suppression occurs with the majority of therapies used to treat BC
 - Management includes myeloid growth factors, transfusions and dose reduction/delay

- An interdisciplinary approach is critical, including specialised oncology and/or breast care nurses to proactively screen for and manage treatment-emergent toxicities
- Patients should be informed about the side-effect profiles of recommended systemic treatments
 - All treatment should include formal patient education regarding side-effect management
- Particular attention must be paid to the risk of side-effects in specific populations, such as elderly patients and those with comorbidities, to ensure therapy adherence
- Proactive symptom management and education helps to alleviate side-effects and improves QoL
- Careful assessment of side-effects should occur at each visit
 - Electronic PROs may be useful in this context
- QoL assessments should be incorporated into treatment efficacy evaluations
- Dose reduction and delay are effective strategies to manage toxicity in advanced disease

Palliative care

- Palliative care should be integrated early and offered in both inpatient and outpatient settings
- Patients should be offered optimal symptom control, psychological, social and spiritual support, in addition to receiving the best available treatment
- Many areas of care need to be managed, including pain, dyspnoea, cachexia, fatigue, depression and anxiety
- Comorbidities, previous treatments, age and patient preferences should also be considered
- Shared decision making between the patient and healthcare professionals, as well as good communication and relationship building with the patient, family members and caregivers, is paramount to ensure a mutual understanding of treatment expectations
- The emotional toll of caring for patients who are dying also has an impact on healthcare staff, and processes should be in place to support their mental health

Patient perspective

- For all patients with BC or MBC, receiving optimal care as part of a multidisciplinary approach is of greatest importance
- Besides access to optimal treatment, patient information and education is particularly important
 - Only well-informed and educated patients can be equally involved in treatment choices, leading to improved treatment outcomes

- A common concern for patients with MBC is that they don't want to suffer cancer-related and/or treatment-related effects
 - For every new line of treatment, patients expect disease progression to stop, but not at any cost
- Patients often emphasise that QoL is more important to them than PFS or OS
 - The definition of good QoL can differ from patient to patient depending on personal preferences, cultural and religious perspectives and age
- In addition to psychosocial support, patient support groups or online closed groups can provide safe places for patients and give them emotional support

HEREDITARY BREAST CANCER SYNDROMES

INCIDENCE AND EPIDEMIOLOGY

- Hereditary breast and ovarian cancer syndrome (HBOC) is defined:
 - Clinically by family history criteria
 - Molecularly by identification of germline pathogenic variants (PVs) in clinically-validated HBOC genes
- HBOC genes are broadly classified as:
 - High-risk genes, which increase cancer risk by at least fourfold
 - Moderate-risk genes, which increase cancer risk by two- to fourfold
- Lifetime cancer risks for HBOC-associated PVs are shown in the table on the next page
- Individuals with significant family history should be offered genetic testing, using multigene panels of clinically-validated HBOC genes
- The genetic basis of around half of clinical HBOCs is currently unknown, or unexplained by single-gene variants
- Conversely, approximately half of individuals who harbour PVs in HBOC genes do not have a suggestive family history
 - Clinicians should be aware that family history-based testing misses about half of HBOC gene carriers
 - Strategies to identify these high-risk individuals are being developed
- HBOC has been estimated to underlie ~10% of breast cancers (BCs)
- Molecularly, ~6% of patients with BC harbour PVs in HBOC genes
 - Half (~3%) in *BRCA1*, *BRCA2* and other high-risk genes [e.g. partner and localiser of *BRCA2* (*PALB2*)]
 - Half (~3%) in moderate-risk genes [e.g. ATM serine/threonine kinase (*ATM*), checkpoint kinase 2 (*CHEK2*)]
- The prevalence of molecular HBOC in unaffected individuals varies based on family history and ethnicity
 - Some populations harbour founder PVs with high carrier frequencies (e.g. 1:40 for *BRCA1* and *BRCA2* PVs in Ashkenazi Jews)
 - Studies carried out in non-founder populations suggest that the carrier frequency for high-risk genes (i.e. *BRCA1*, *BRCA2*, *PALB2*) is approximately 1:150

LIFETIME CANCER RISKS FOR HBOC-ASSOCIATED PVS

	BC*	TUBO-OVARIAN CANCERS†	PANCREATIC CANCER‡	COLON CANCER§	OTHER CANCERS
<i>ATM</i>	Yes 25-30%	Yes < 5%	Yes < 5%	No	Prostate: 30%
<i>BARD1</i>	Yes ~20%	No	No	No	No
<i>BRCA1</i>	Yes > 60%	Yes 40-60%	Yes < 5%	No	
<i>BRCA2</i>	Yes > 60%	Yes 15-30%	Yes < 5%	No	Prostate: 33%
<i>BRIP1</i>	No	Yes 5-10%	No	No	No
<i>CDH1</i>	Yes (LBC) 40%	No	No	No	Diffuse gastric cancer: 35-45%
<i>CHEK2</i>	Yes 25-30%	No	No	Yes 15%	
<i>PALB2</i>	Yes 40-60%	Yes 3-5%	Yes 2-3%	No	No
<i>PTEN</i>	Yes 40%	No	No	Yes 10%	Thyroid: 20% Endometrial: 20%
<i>RAD51C</i>	Yes 20%	Yes 10%	No	No	No
<i>RAD51D</i>	Yes 10%	Yes 10%	No	No	No
<i>STK11</i>	Yes 40%	No	Yes 10-30%	Yes 30%	Gastric: 30% Sertoli-Leydig: 10-20%
<i>TP53</i>	Yes 40%	No	Possibly	Possibly	Sarcoma, brain, leukaemia, adrenocortical carcinoma

Lifetime risk in general “average risk” population: *BC 11%, †ovarian cancer 1.3%, ‡pancreatic cancer 1.6%, §colon cancer 4%
ATM, ATM serine/threonine kinase; *BARD1*, *BRCA1* associated ring domain 1; BC, breast cancer; *BRIP1*, *BRCA1* interacting helicase 1; *CDH1*, cadherin 1; *CHEK2*, checkpoint kinase 2; HBOC, hereditary breast and ovarian cancer syndrome; LBC, lobular breast cancer; *PALB2*, partner and localiser of *BRCA2*; *PTEN*, phosphatase and tensin homologue; PV, pathogenic variant; *RAD51C*, *RAD51* paralogue C; *RAD51D*, *RAD51* paralogue D; *STK11*, serine/threonine kinase 11; *TP53*, tumour suppressor protein p53

POST-TEST COUNSELLING AND FOLLOW-UP OF INDIVIDUALS WITH HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

Genetic counselling

- Post-test genetic counselling should include discussion of the medical and psychological implications for the individual and their family
 - Medical implications include the impact on treatment of any current cancer and interventions for prevention or early detection of future cancers
- Risk assessment should be comprehensive and individualised, taking into account the specific gene and variant identified, as well as other individual non-genetic (e.g. age, reproductive history) and genetic risk factors
- When available, validated tools such as CanRisk (<https://www.canrisk.org/>) should be used to aid decision making
- Counselling must include clear explanations of the familial implications, indicating which relatives (both female and male) need to be informed and offered counselling and testing
 - Enhancing awareness and availability of testing in at-risk relatives should be a priority

Follow-up

- Follow-up is lifelong for individuals with HBOC and may involve serial imaging, risk-reducing surgery, risk-reducing medication (RRMed) and quality of life issues
- Risk management should be carried out in specialised high-risk clinics that are multidisciplinary and should include psychologists, if possible

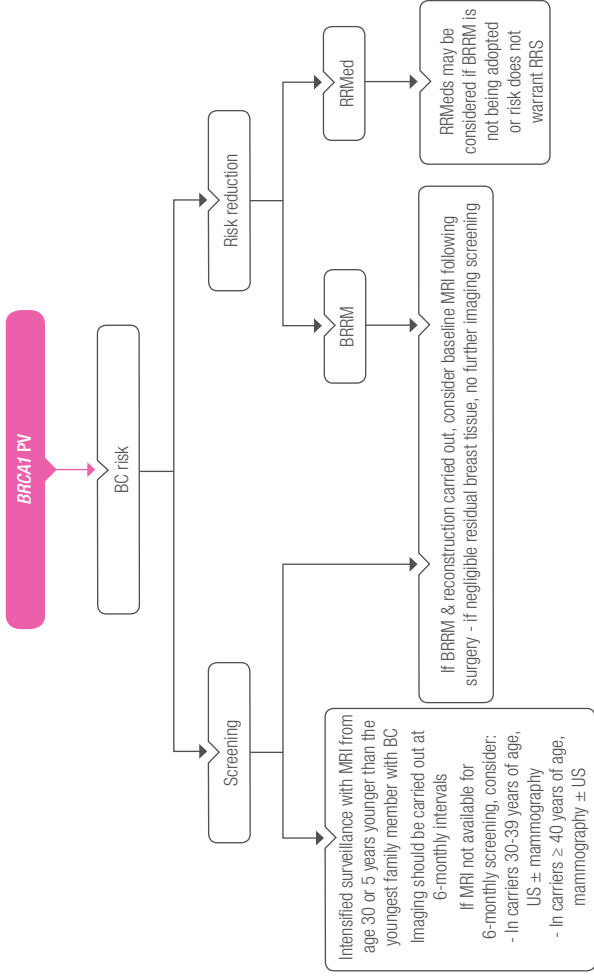
BREAST CANCER RISK MANAGEMENT

- Recommendations for BC screening and risk reduction in carriers of *BRCA1* and *BRCA2* PVs are shown in the figures on the next pages

Screening for women with high-risk pathogenic variants

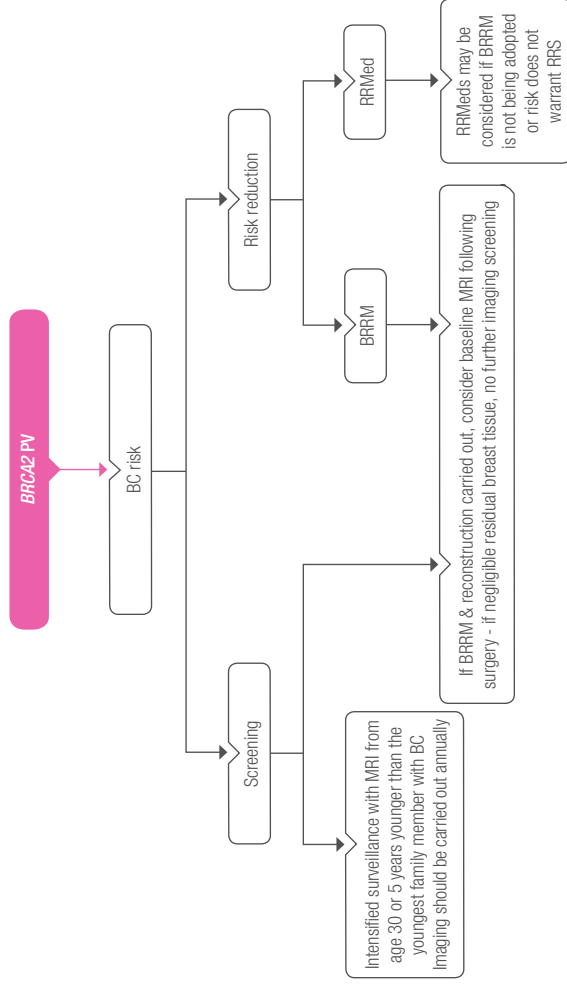
- Women with HBOC should be offered intensified screening if they do not opt for a risk-reducing mastectomy (RRM)
- In women with PVs in *BRCA1*, *BRCA2* or *PALB2*, intensified screening should start at the age of 30 or 5 years earlier than the age at diagnosis of the youngest family member with BC
- Breast magnetic resonance imaging (MRI) should be considered the essential component of intensified screening programmes
 - Clinical breast examination is of no value as a screening tool
- Annual screening intervals are recommended, except for *BRCA1* PV carriers, in which 6-monthly screening should be considered

BC SCREENING AND RISK REDUCTION IN CARRIERS OF *BRCA1* PVS



BC, breast cancer; BRRM, bilateral risk-reducing mastectomy; MRI, magnetic resonance imaging; PV, pathogenic variant; RRMed, risk-reducing medication; RRS, risk-reducing surgery; US, ultrasound

BC SCREENING AND RISK REDUCTION IN CARRIERS OF *BRCA2* PVS



BC, breast cancer; BRRM, bilateral risk-reducing mastectomy; MRI, magnetic resonance imaging; PV, pathogenic variant; RRMed, risk-reducing medication; RRS, risk-reducing surgery

- If 6-monthly screening is considered, this may be best achieved with an annual MRI and (depending on availability, resources and local guidelines) the following imaging between MRIs:
 - Ultrasound (US) with or without mammography in carriers 30-39 years of age
 - Mammography with or without US in carriers ≥ 40 years of age
- There is currently no evidence to base a recommendation on the appropriate end date of intensified screening
 - The decision may be based on individual factors such as breast density, comorbidities and the patient's priorities
- There is no evidence to support continued routine breast imaging after RRM. However, it is reasonable to carry out a baseline MRI in the first year after RRM to evaluate the amount of residual breast tissue, with further decisions on imaging screening made on a case-by-case basis
- Intensified screening should continue after breast-conserving treatment or unilateral mastectomy for non-metastatic hereditary BC
- Intensified breast screening should be considered in women with ovarian cancer who have no evidence of recurrence in a prolonged remission
- There should be rigorous quality assurance of intensified screening programmes, including benchmarking of programme sensitivity, false-positive rates, recall rates and availability of MRI-guided biopsy

Lifestyle factors and breast cancer risk

- Physical exercise most days at moderate or strenuous intensity should be encouraged if appropriate (more is better)
 - Individuals should avoid being overweight or obese
 - Breastfeeding should be encouraged
- Alcohol is associated with an increased risk for BC in the general population
 - Although studies have not demonstrated a clear association for *BRCA1/2* PV carriers, individuals should be advised to minimise alcohol intake
- Use of hormonal contraception and combined hormone replacement therapy are associated with increased BC risk in the general population, but it is not clear if this is also true for *BRCA1/2* PV carriers
 - Decisions about hormonal contraception should balance the possible increase in BC risk against contraceptive efficacy, convenience and reduction in risk of ovarian cancer

Risk-reducing medication

- RRM can be considered for primary risk reduction of BC and risk reduction of contralateral disease in women who decline bilateral risk-reducing mastectomy (BRRM) or who have a risk level that does not warrant surgery
 - Data pertaining specifically to women with PVs in germline predisposition genes are extremely limited
- RRMeds include selective oestrogen receptor modulators (e.g. tamoxifen, raloxifene) and aromatase inhibitors (e.g. anastrozole, exemestane)
 - Tamoxifen is the only option for premenopausal women
 - Side-effect profiles should be considered when choosing between agents for postmenopausal women (including increased risk of thrombosis, endometrial cancer and osteoporosis)

Risk-reducing surgery

- BRRM is the most effective method for reducing BC risk for *BRCA1/2* PV carriers
- BRRM should be discussed in carriers of other high-risk genes [tumour suppressor protein p53 (*TP53*), phosphatase and tensin homologue (*PTEN*), serine/threonine kinase 11 (*STK11*), cadherin 1 (*CDH1*) and *PALB2*] alongside family history
- BRRM is an extensive procedure that should be carefully discussed, taking into consideration the benefits, complications and psychosocial impact
- A variety of BRRM techniques exist, from total mastectomy (TM) to skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM), which aim to improve cosmetic results
 - Limited data suggest that NSM provides similar risk reduction and possibly superior cosmetic outcomes compared with TM or SSM; therefore, NSM is a reasonable alternative to TM
- Immediate reconstruction is safe and should be offered
- In all affected high-risk PV carriers, contralateral RRM lessens the incidence of contralateral BC without a proven impact on overall survival
- In women with stage I-III high-risk PV-associated BC (not including *TP53*), breast-conservation with therapeutic radiation is a safe alternative to RRM
- RRM may be considered on a case-by-case basis in women with ovarian cancer who have no evidence of recurrence in a prolonged remission

Approach to male carriers of high-risk pathogenic variants

- There is evidence of an increased risk in male BC for nearly all HBOC genes; the most compelling data is for men harbouring *BRCA2* PVs

- Annual mammography or US screening should be considered in male *BRCA2* PV carriers with additional high-risk features such as gynaecomastia or Klinefelter syndrome
 - Screening should begin from the age of 50 years or 10 years earlier than the age at diagnosis of the youngest male family member with BC
- Male *BRCA2* PV carriers should be encouraged to be aware of physical changes in the breast and to seek medical attention accordingly

Screening for additional malignancies

- Screening with annual contrast enhanced MRI and/or endoscopic US from age 50 (or 5-10 years younger than the affected relative) may be considered in *BRCA1*, *BRCA2*, *ATM*, *TP53* or *PALB2* carriers with at least one first- or second-degree relative with exocrine pancreatic cancer
- Annual blood prostate-specific antigen screening should be offered to male *BRCA2* carriers from the age of 40 years and may be considered for male *ATM* carriers from the age of 40 years

COUNSELLING, RISK-REDUCTION AND SCREENING IN THE PRESENCE OF OTHER MODERATE-HIGH RISK PATHOGENIC VARIANTS

- Genetic testing for HBOC susceptibility often incorporates screening for PVs in genes beyond *BRCA1* and *BRCA2*
 - The associated cancer risks vary widely between genes, as do the approaches to screening and risk reduction
 - It is important to differentiate “other genes” from *BRCA1* and *BRCA2* during counselling
- In the presence of *CDH1*, *PTEN* or *STK11* PVs, intensified breast screening should start at the age of 30 years or 5 years earlier than the age at diagnosis of the youngest family member with BC; screening should start from the age of 20 years for *TP53* PV carriers
 - BRRM may be discussed on a case-by-case basis
- Women with PVs in *ATM*, *BRCA1* associated ring domain 1 (*BARD1*), *CHEK2* (truncating), *RAD51* paralogue C (*RAD51C*) or *RAD51* paralogue D (*RAD51D*) should undergo comprehensive, individualised assessment of BC risk to determine their eligibility for breast MRI
- Validated risk assessment tools, such as CanRisk, may be used to aid individual risk management

REPRODUCTIVE AND ENDOCRINOLOGICAL ISSUES IN INDIVIDUALS WITH HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

Contraception

- While hormone-based forms of contraception are not contraindicated, unaffected carriers should be offered non-hormonal forms of contraception when feasible and should minimise prolonged periods of exposure to exogenous hormones
- In women considering tamoxifen chemoprevention, concurrent use of the oral contraceptive pill is contraindicated due to the elevated risk of venous thromboembolism

Fertility

- Healthy female carriers should be encouraged to complete childbearing before the recommended age for risk-reducing bilateral salpingo-oophorectomy (RRBSO); if this is not feasible, oocyte and embryo cryopreservation can be offered at a young age
- Individuals with highly penetrant cancer susceptibility syndromes should be informed about prenatal diagnosis or preimplantation genetic testing (PGT), which may be used to avoid passing on the hereditary PV to future offspring
 - The pros and cons of these strategies should be clearly discussed, including potential pregnancy termination in the case of prenatal diagnosis and the need for *in vitro* fertilisation strategies with PGT
 - Religious, cultural, ethical and socioeconomic issues, as well as country/centre availability, are important factors affecting the individual's choice to access these technologies

Management of menopausal symptoms

- In unaffected *BRCA1/2* carriers, discussing limitations and risks, short-term use of HRT after RRBSO may be considered to alleviate menopausal symptoms
- Bone assessment should be considered, tailored to individual risk factors. Preventive/therapeutic measures should be considered as indicated
- Low-dose intra-vaginal oestrogens may be considered to manage genitourinary symptoms of menopause

UNIQUE PSYCHOLOGICAL ISSUES FOR INDIVIDUALS WITH HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

- Observational studies of the psychological impact of HBOC have provided highly variable results
 - Some carriers experience elevated and sustained levels of psychological distress
 - Individual risk factors include high levels of anxiety and depression prior to genetic testing, cancer diagnosis, being unpartnered and a family history of cancer

- The negative effects of BRRM can include distress about loss of sensation and discomfort with reconstructed breasts, as well as decreased perceived attractiveness and femininity
- Notable risk factors for decreased body image include poor reconstruction outcomes, surgical complications and lack of information prior to surgery
- The need for further information and emotional support should be assessed before disclosure of genetic test results, and individuals should be offered referrals for psychological counselling and/or further support
- Sexual health concerns should be assessed, and individuals should be offered support and resources, as needed, to address sexual dysfunction. Individuals should be asked about sexual health concerns regardless of age, partner status or sexual orientation

PERSONALISED MEDICINE AND FUTURE DIRECTIONS

- Germline genetic testing has led to improvements in screening, risk reduction and therapies for those with inherited cancer susceptibility; however, there is a need for more individualised risk assessment to inform the timing and type of risk-reduction strategies, such as RRM, and for optimal risk management in moderate penetrance genes
- Single nucleotide polymorphisms (SNPs) have been well validated to alter cancer risk, both in the general population and in those with inherited cancer susceptibility
 - A polygenic risk score (PRS) captures the risk associated with SNPs and can be used in models such as CanRisk
 - A PRS may be particularly important in individuals with inherited PVs in *ATM* or *CHEK2* as some of these individuals will have a close to average risk of BC and others will have a higher risk
 - Modification by PRS is likely to become increasingly important as individuals without a strong family history of cancer undergo genetic testing
- Another emerging field is early detection using liquid biopsies targeting tumour-derived mutational, epigenetic or transcriptomic features
- Use of PRSs, novel risk-reduction strategies and liquid biopsy assays for early detection should continue to be performed and assessed in the context of clinical trials

EARLY BREAST CANCER

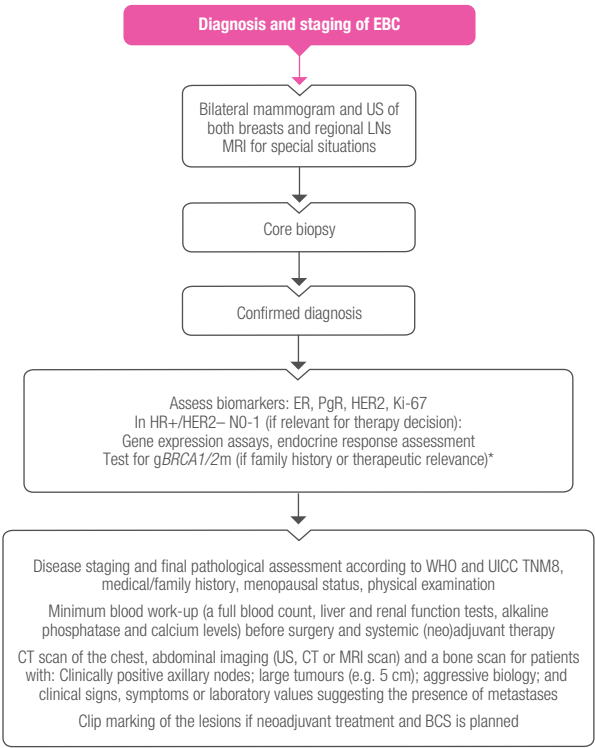
SCREENING

- Regular (every 2 years) mammography is recommended in average-risk women 50-69 years of age. Regular mammography may also be carried out in women 45-49 and 70-74 years, although there is less evidence of benefit
- Screening in women with a strong family history or known germline *BRCA1/2* mutations (g*BRCA1/2*m) and other high-risk pathogenic variants (PVs) should follow the ESMO Clinical Practice Guideline (CPG) for risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes (<https://www.esmo.org/guidelines/guidelines-by-topic/hereditary-syndromes/risk-reduction-screening-hereditary-breast-ovarian-cancer-syndromes>)

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

- A proposed algorithm for the diagnostic work-up and staging of early breast cancer (EBC) is shown in the figure on the next page
- Diagnostic work-up is based on clinical examination and imaging, including bilateral mammography and ultrasound (US) of both breasts and regional lymph nodes (LNs) or two-dimensional digital mammography in the symptomatic setting
- Digital breast tomosynthesis (with or without synthetic mammography) and contrast-enhanced mammography can be considered as alternatives, where available and appropriate
- Magnetic resonance imaging (MRI) is recommended in case of uncertainties following standard imaging and in special clinical situations (e.g. familial breast cancer associated with g*BRCA1/2*m and other high-risk PVs, lobular cancers, suspicion of multifocality and/or multicentricity, presence of breast implants)
- Assessment of distant metastases (bone, liver and lung) is recommended only in patients with a high risk of recurrence at first diagnosis and in symptomatic patients
- Pre-treatment pathological assessment, including a complete histomorphological, immunohistochemical and molecular assessment, if applicable, is recommended at the time of diagnosis and should include primary tumour histology and axillary node histology/cytology (if node involvement is suspected clinically)
- A summary of biomarkers used in the standardised histopathological, immunohistochemical and molecular pathology assessment in EBC is shown in the table on pages 41 & 42

DIAGNOSTIC WORK-UP AND STAGING OF EBC



*Detailed rationale for gBRCA1/2m testing is covered in the ESMO CPG for risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes (<https://www.esmo.org/guidelines/guidelines-by-topic/hereditary-syndromes/risk-reduction-screening-hereditary-breast-ovarian-syndromes>)

BCS, breast-conserving surgery; CPG, Clinical Practice Guideline; CT, computed tomography; EBC, early breast cancer; ER, oestrogen receptor; ESMO, European Society for Medical Oncology; gBRCA1/2m, germline BRCA1/2 mutation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LN, lymph node; MRI, magnetic resonance imaging; N, node; PgR, progesterone receptor; TNM8, tumour–node–metastasis eighth edition; UICC, Union for International Cancer Control; US, ultrasound; WHO, World Health Organization

SUMMARY OF BIOMARKERS USED IN STANDARDISED HISTOPATHOLOGICAL, IMMUNOHISTOCHEMICAL AND MOLECULAR PATHOLOGY ASSESSMENT IN EBC

METHOD	BIOMARKER	USE	COMMENTS, PITFALLS AND OPEN QUESTIONS
Biomarkers currently used in EBC			
Classical H&E pathology	Histological tumour type, invasiveness, grading, TILs	Pathological diagnosis and basic prognostic characterisation of tumour	TILs are not currently required for therapy decisions but might become relevant in the future
IHC and ISH	IHC panel: ER, PgR, HER2, Ki-67 ISH: For HER2 IHC 2+ Defined guidelines for each marker; participation in external quality assurance programmes	Standard IHC work-up as a basis for major therapy decisions and prognostic assessment Definition of intrinsic subtypes	HR-low tumours (ER/PgR 1-9%) are biologically TNBC and may behave as such HER2 status should be reported as IHC 0, 1+ or 2+ (either negative or positive by ISH) and 3+ HER2-low tumours (1+ or 2+ with negative ISH) are relevant for MBC and may become so for EBC in the future Ki-67 may be evaluated after a short course of preoperative ET to indicate endocrine responsiveness (Ki-67 ≤ 10%)
Gene expression profiling (many different validated test options)	Gene signatures	Validated prognostic assessment	May be carried out in HR+, HER2– tumours in the intermediate risk category (defined by IHC and clinical assessment) May be carried out in diagnostic core biopsy
NGS	Germline PVs/mutations	Clinically important information for surgical management, follow-up and cancer screening, and has become a patient selection marker for systemic adjuvant olaparib therapy in HER2– tumours	Testing is relevant for TNBC and HR+, HER2– breast cancer

METHOD	BIOMARKER	USE	COMMENTS, PITFALLS AND OPEN QUESTIONS
Biomarkers currently not mandatory in EBC			
IHC	PD-L1	Standardised methodology and validated antibodies Reporting of different scoring systems (immune cell staining; CPS) in parallel	Not relevant for therapy decisions in EBC. Relevant in metastatic TNBC only. For treatment decisions, testing can be carried out in the primary breast tumour or the most recent metastasis
NGS - tumour	Mutations in <i>PIK3CA</i> , <i>ESR1</i> , <i>HER2</i> , <i>BRCA1/2</i> and other genes	Biomarkers for therapeutic strategies in the metastatic setting	Relevant in metastatic disease only

CPS, combined positive score; EBC, early breast cancer; ER, oestrogen receptor; *ESR1*, oestrogen receptor 1; ET, endocrine therapy; H&E, haematoxylin–eosin; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, *in situ* hybridisation; MBC, metastatic breast cancer; NGS, next-generation sequencing; PD-L1, programmed death–ligand 1; PgR, progesterone receptor; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PV, pathogenic variant; TIL, tumour-infiltrating lymphocyte; TNBC, triple-negative breast cancer

- Assessment should include histological type, grade and immunohistochemistry (IHC) evaluation of oestrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) biomarkers and a proliferation marker such as Ki-67. Fluorescence *in situ* hybridisation testing should be carried out in cases of an equivocal HER2 IHC score (HER2 2+)
- For histological assessment, a core needle biopsy is preferred to fine-needle aspiration (FNA) because invasiveness (a prerequisite for starting neoadjuvant therapy) cannot be demonstrated in FNA samples
- For prognostication and treatment decision making, tumours should be grouped into biological subtypes, defined by routine histology and IHC results, as luminal A, luminal B, HER2-positive and triple-negative
- In cases of hormone receptor (HR)-positive, HER2-negative EBC with uncertainty about indications for adjuvant chemotherapy (ChT) (after consideration of all clinical and pathological factors), gene expression assays and endocrine response assessment in the preoperative setting can be used
- HER2-negative, HR-low (i.e. 1–9% ER and/or PgR expression) tumours are a heterogeneous group, some of which behave biologically similarly to triple-negative breast cancer (TNBC)
- HER2-low status is currently only relevant in the metastatic setting, but HER2 should be reported as 0, 1+, 2+ or 3+ in EBC as a basis for possible future therapeutic decisions

- Tumour-infiltrating lymphocytes (TILs) may add prognostic and predictive information, particularly in TNBC and HER2-positive breast cancer, but there are no distinct TIL thresholds for treatment decisions
- Programmed death–ligand 1 expression levels **should not** be used to guide immunotherapy treatment decisions in early TNBC
- Germline testing and subsequent genetic counselling for PVs in *BRCA1/2* should be offered to patients who meet the respective national criteria and to those who are candidates for adjuvant olaparib therapy

STAGING AND RISK ASSESSMENT

- Disease stage and final pathological and clinical assessment of surgical specimens should be made according to the World Health Organization (WHO) classification of tumours and the eighth edition of the Union for International Cancer Control (UICC) tumour–node–metastasis (TNM) staging system, as shown in the tables below and on the next pages

CLINICAL CLASSIFICATION OF BREAST TUMOURS ACCORDING TO THE UICC TNM EIGHTH EDITION

PRIMARY TUMOUR (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma <i>in situ</i>
Tis (DCIS)	Ductal carcinoma <i>in situ</i>
Tis (LCIS)	Lobular carcinoma <i>in situ</i>
Tis (Paget)	Paget disease of the nipple not associated with invasive carcinoma and/or carcinoma <i>in situ</i> (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorised based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted
T1	Tumour ≤ 2 cm in greatest dimension
T1mi	Microinvasion ≤ 0.1 cm in greatest dimension*
T1a	> 0.1 cm but ≤ 0.5 cm in greatest dimension
T1b	> 0.5 cm but ≤ 1 cm in greatest dimension
T1c	> 1 cm but ≤ 2 cm in greatest dimension

PRIMARY TUMOUR (T)	
T2	Tumour > 2 cm but ≤ 5 cm in greatest dimension
T3	Tumour > 5 cm in greatest dimension
T4	Tumour of any size with direct extension to chest wall and/or to skin (ulceration or skin nodules) [†]
T4a	Extension to chest wall (does not include pectoralis muscle invasion only)
T4b	Ulceration, ipsilateral satellite skin nodules or skin oedema (including peau d'orange)
T4c	Both 4a and 4b
T4d	Inflammatory carcinoma [‡]
REGIONAL LNs (N)	
NX	Regional LNs cannot be assessed (e.g. previously removed)
N0	No regional LN metastasis
N1	Metastasis in movable ipsilateral level I, II ALN(s)
N2	Metastasis in ipsilateral level I, II ALN(s) that are clinically fixed or matted; or in clinically detected [§] ipsilateral internal mammary LN(s) in the absence of clinically evident ALN metastasis
N2a	Metastasis in ALN(s) fixed to one another (matted) or to other structures
N2b	Metastasis only in clinically detected [§] internal mammary LN(s) and in the absence of clinically detected ALN metastasis
N3	Metastasis in ipsilateral infraclavicular (level III axillary) LN(s) with or without level I, II ALN involvement; or in clinically detected [§] ipsilateral internal mammary LN(s) with clinically evident level I, II ALN metastasis; or metastasis in ipsilateral supraclavicular LN(s) with or without axillary or internal mammary LN involvement
N3a	Metastasis in infraclavicular LN(s)
N3b	Metastasis in internal mammary and ALNs
N3c	Metastasis in supraclavicular LN(s)

DISTANT METASTASIS (M)	
M0	No distant metastasis
M1	Distant metastasis

Excisional biopsy of a LN or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, e.g. cN1. Pathological classification (pN) is used for excision or sentinel LN biopsy only in conjunction with a pathological T assignment. [†]Microinvasion is the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus > 0.1 cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion. Do not use the sum of all individual foci. The presence of multiple foci of microinvasion should be noted, as it is with multiple larger invasive carcinomas.

[‡]Invasion of the dermis alone does not qualify as T4. Chest wall includes ribs, intercostal muscles and serratus anterior muscle but not pectoral muscle

[§]Inflammatory carcinoma of the breast is characterised by diffuse, brawny induration of the skin with an erysipeloid edge, usually with no underlying mass. If the skin biopsy is negative and there is no localised measurable primary cancer, the T category is pTX when pathologically staging a clinical inflammatory carcinoma (T4d). Dimpling of the skin, nipple retraction or other skin changes, except those in T4b and T4d, may occur in T1, T2 or T3 without affecting the classification

[¶]Clinically detected is defined as detected by clinical examination or by imaging studies (excluding lymphoscintigraphy) and having characteristics highly suspicious for malignancy or a presumed pathological macrometastasis based on FNA biopsy with cytological examination. Confirmation of clinically detected metastatic disease by FNA without excision biopsy is designated with a (f) suffix, e.g. cN3a(f)

ALN, axillary lymph node; c, clinical; DCIS, ductal carcinoma *in situ*; FNA, fine-needle aspiration; LCIS, lobular carcinoma *in situ*; LN, lymph node; p, pathological; M, metastasis; N, node; T, tumour; Tis, carcinoma *in situ*; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control

Brierley JD et al, eds. *TNM Classification of Malignant Tumours*, 8th edition. Oxford: John Wiley & Sons, Inc. 2016. Reprinted with permission from John Wiley & Sons, Ltd

PATHOLOGICAL CLASSIFICATION OF BREAST TUMOURS ACCORDING TO THE UICC pTNM EIGHTH EDITION

PRIMARY TUMOUR (pT)

The pathological classification requires the examination of the primary carcinoma with no gross tumour at the margins of resection. A case can be classified pT if there is only microscopic tumour in a margin. The pT categories correspond to the T categories*

REGIONAL LNs (pN)

The pathological classification requires the resection and examination of at least the low ALNs (level I). Such a resection will ordinarily include ≥ 6 LNs. If the LNs are negative, but the number ordinarily examined is not met, classify as pN0

pNX	Regional LNs cannot be assessed (e.g. previously removed, or not removed for pathological study)
pN0	No regional LN metastasis [†]
pN1	Micrometastases; or metastases in 1–3 axillary ipsilateral LNs; and/or in internal mammary nodes with metastases detected by SLNB but not clinically detected [‡]

REGIONAL LNs (pN)	
pN1mi	Micrometastases (> 0.2 mm and/or > 200 cells, but none > 2.0 mm)
pN1a	Metastasis in 1-3 axillary LN(s), including at least one > 2 mm in greatest dimension
pN1b	Internal mammary LNs
pN1c	Metastasis in 1-3 ALNs and internal mammary LNs
pN2	Metastasis in 4-9 ipsilateral ALNs, or in clinically detected [†] ipsilateral internal mammary LN(s) in the absence of ALN metastasis
pN2a	Metastasis in 4-9 axillary LNs, including at least one that is > 2 mm
pN2b	Metastasis in clinically detected internal mammary LN(s), in the absence of ALN metastasis
pN3a	Metastasis in ≥ 10 ipsilateral ALNs (at least one > 2 mm) or metastasis in infraclavicular LNs
pN3b	Metastasis in clinically detected [†] internal ipsilateral mammary LN(s) in the presence of positive ALN(s); or metastasis in > 3 ALNs and in internal mammary LNs with microscopic or macroscopic metastasis detected by SLNB but not clinically detected
pN3c	Metastasis in ipsilateral supraclavicular LN(s)
POST-TREATMENT ypN	
Post-treatment yp 'N' should be evaluated as for clinical (pre-treatment) 'N' methods. The modifier 'sn' is used only if a SN evaluation was carried out after treatment. If no subscript is attached, it is assumed the axillary nodal evaluation was by axillary node dissection	
The X classification will be used (ypNX) if no yp post-treatment SN or axillary dissection was carried out	
N categories are the same as those used for pN	

*When classifying pT, the tumour size is a measurement of the invasive component. If there is a large *in situ* component (e.g. 4 cm) and a small invasive component (e.g. 0.5 cm), the tumour is coded pT1a

[†]ITCs are single tumour cells or small clusters of cells ≤ 0.2 mm in greatest extent that can be detected by routine H&E stains or IHC. An additional criterion has been proposed to include a cluster of < 200 cells in a single histological cross section. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification and should be included in the total number of nodes evaluated

[†]Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathological macrometastasis based on FNA biopsy with cytological examination. Not clinically detected is defined as not detected by imaging studies (excluding lymphoscintigraphy) or clinical examination

ALN, axillary lymph node; FNA, fine-needle aspiration; H&E, haematoxylin-eosin; IHC, immunohistochemistry; ITC, isolated tumour cell; LN, lymph node; N, node; p, pathological; SLNB, sentinel lymph node biopsy; SN, sentinel node; T, tumour;

TNM, tumour–node–metastasis; UICC, Union for International Cancer Control; yp, post-neoadjuvant pathological
 Brierley JD et al, eds. *TNM Classification of Malignant Tumours*, 8th edition. Oxford: John Wiley & Sons, Inc. 2016. Reprinted with permission from John Wiley & Sons, Ltd

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

*T1 includes T1mi
 mi, micrometastases; M, metastasis; N, node; T, tumour; Tis, carcinoma *in situ*; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control
 Brierley JD et al, eds. *TNM Classification of Malignant Tumours*, 8th edition. Oxford: John Wiley & Sons, Inc. 2016. Reprinted with permission from John Wiley & Sons, Ltd

- Minimum blood work-up (a full blood count, liver and renal function tests, alkaline phosphatase and calcium levels) is recommended before surgery and systemic (neo)adjuvant therapy
- A computed tomography (CT) scan of the chest, abdominal imaging (US, CT or MRI scan) and a bone scan can be considered for patients with:
 - Clinically positive axillary nodes
 - Large tumours (e.g. 5 cm)
 - Aggressive biology
 - Clinical signs, symptoms or laboratory values suggesting the presence of metastases

- The complete medical and family history must be evaluated, including menopausal status (if in doubt, serum oestradiol and follicle-stimulating hormone levels should be measured)
- [¹⁸F]2-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET)-CT scanning may be used instead of CT and bone scintigraphy, particularly for high-risk patients and when conventional methods are inconclusive

MANAGEMENT OF EARLY BREAST CANCER

General treatment principles

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

Patient communication and shared decision making

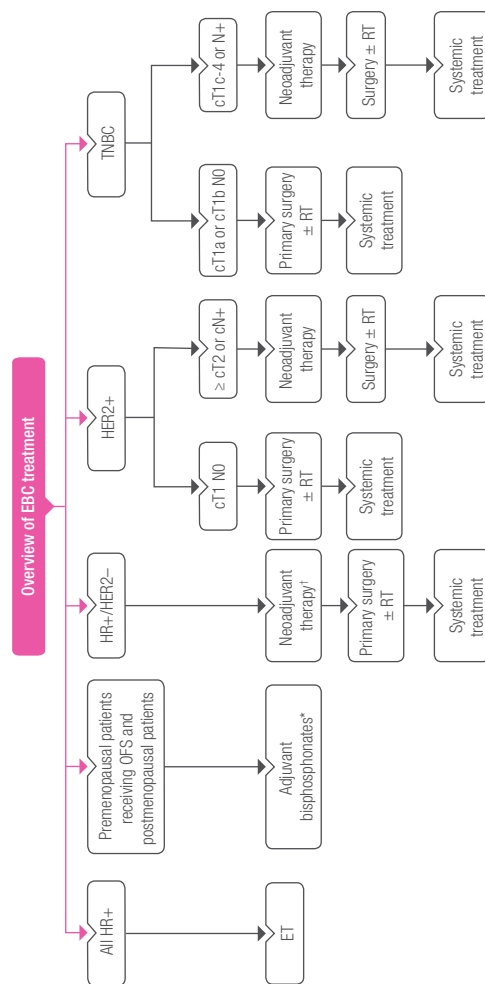
- Information on diagnosis and treatment choice should be given repeatedly (both verbally and in writing) in a comprehensive and easily understandable manner
- The use of reliable, patient-centred websites or similar sources of information is recommended
- Patients should be actively involved in all treatment decisions and should have equitable access to the full range of reproductive care options including pregnancy counselling, contraception and fertility preservation

Locoregional treatment

Surgery

- Breast-conserving surgery (BCS) with postoperative radiotherapy (RT) is the preferred local treatment option for the majority of patients with EBC

OVERVIEW OF EBC MANAGEMENT



*Bisphosphonates are approved for treating bone metastases and osteoporosis and not for prevention of relapse

†If cT1c is indicated it may be given in the neoadjuvant setting

c, clinical; ChT, chemotherapy; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; N, node; OFS, ovarian function suppression; T, tumour; TNBC, triple-negative breast cancer; RT, radiotherapy

*Discuss in MDT whether number of LNs is important for systemic therapy allocation

[†]See figure on page 49 for an overview of primary surgery and neoadjuvant therapy indications

[‡]Imaging (axillary US is preferred but MRI and PET-CT may be used in specific cases where more detailed imaging is required)

[§]Refers to ACOSOG-20011 trial eligibility criteria

^{||}Refers to AMAROS trial eligibility criteria. OTOASOR trial criteria can also be considered

[¶]Inflammatory breast cancer and patients with N2 or N3 stage disease should receive ALND unless otherwise defined in a clinical trial

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

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

- PMRT should be considered in patients with intermediate-risk features (e.g. lymphovascular invasion, age), including those with 1-3 positive ALNs
- Nodal RT is recommended for patients with involved LNs (the extent of target volumes depends on risk factors including the number of involved LNs, N stage and response to PST)
- If indicated, PMRT can be administered after immediate breast reconstruction

Systemic treatment

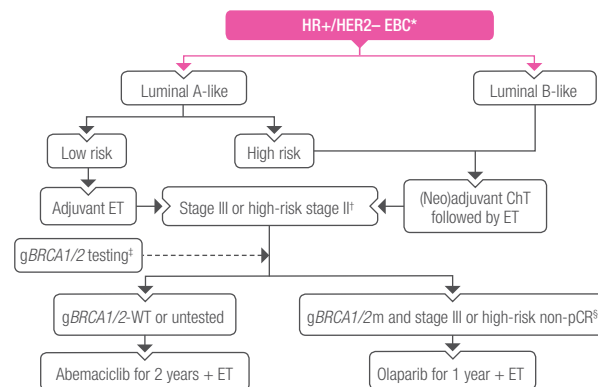
Neo(adjuvant) systemic therapy

- Neoadjuvant therapy should start as soon as diagnosis and staging are completed, ideally within 2-4 weeks
- Adjuvant systemic therapy should be started without undue delays, ideally within 4-6 weeks
- Whenever adjuvant ChT is indicated, neoadjuvant use of the same regimen can also be considered
- The use of dose-dense schedules of ChT, with granulocyte colony-stimulating factor support, should be considered given their documented benefit over non-dose-dense schedules

HR-positive, HER2-negative EBC

- Recommendations for the management of HR-positive, HER2-negative EBC are shown in the figure opposite
 - The role of endocrine therapy (ET) in HR+ EBC is also illustrated
- An overview of adjuvant therapy for patients with HR-positive, HER2-negative EBC is provided in the table on page 54
- All luminal-like breast cancers should be treated with ET
- Most luminal A-like tumours do not require ChT, except those with high disease burden

SYSTEMIC TREATMENT OF HR-POSITIVE, HER2-NEGATIVE EBC



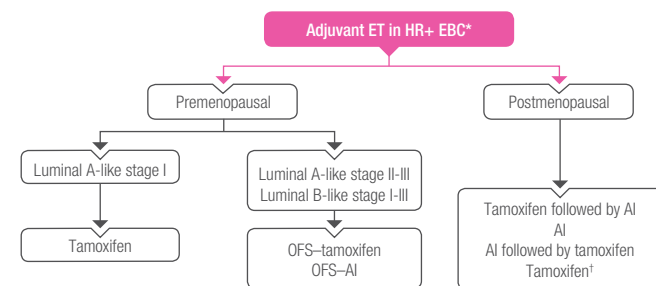
*See figure on page 49 for the role of surgery in HR-positive, HER2-negative EBC

[†]Stage N1 with primary tumour > 5 cm, and/or grade 3 and/or Ki-67 ≥ 20%

[‡]If gBRCA1/2 testing is appropriate and feasible

[§]Patients with HR-positive tumours and non-pCR after neoadjuvant ChT require a CPS+EG score ≥ 3 to receive olaparib
ChT, chemotherapy; CPS+EG, pre-treatment clinical stage and post-treatment pathological stage, oestrogen receptor and tumour grade; EBC, early breast cancer; ET, endocrine therapy; gBRCA1/2, germline BRCA1/2; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; m, mutation; N, node; pCR, pathological complete response; WT, wild type

ROLE OF ADJUVANT ET IN HR-POSITIVE EBC



*See figure on page 49 for the role of surgery in HR-positive, HER2-negative EBC

[†]Tamoxifen can be given for lower-risk tumours or if AIs are not tolerated

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

STAGE	TN	ET*		ChT†	TARGETED THERAPIES			BISPHOSPHONATES†
		Type	Duration of treatment (years)		Addition of OFS in premenopausal women	Premenopausal§	Postmenopausal	
I	T1ab N0	Tamoxifen or AI	5	No††	No††	No	No	No
	T1c N0	Tamoxifen or AI	5	May consider for higher risk††	Low risk††: May consider especially if not receiving OFS High risk††: Yes	No	No	No
II	T2-3 N0	Tamoxifen or AI	7-10	Consider††	Low risk††: Consider especially if not receiving OFS High risk††: Yes	No	No	Yes
	T1-T2 N1	Tamoxifen or AI	7-10	Yes††	Low risk††: Consider especially if not receiving OFS High risk††: Yes	Consider	Low risk††: No Higher risk††: Yes	Yes
III	Any	AI§§	7-10	Yes††	Yes	Yes	Yes	Yes

*Risk stratification factors for ET include tumour size, extent of nodal involvement, tumour grade, degree of ER/PgR expression, high Ki-67 or other proliferation measures and adverse genomic signature results. For lower-risk cancers, either tamoxifen or an AI for 5 years is standard. With increased risk, AI becomes preferred to tamoxifen, longer durations become appropriate and OFS is progressively added for younger women, especially those < 35 years of age

†For node-negative tumours, non-anthracycline regimens may suffice as adjuvant ChT; anthracycline-, taxane- and alkylator-based regimens are preferred for higher-stage cancers warranting ChT

‡As adjuvant therapy for purposes of preventing distant metastatic recurrence

§Benefits of ChT reflect tumour biology and menopausal status. Premenopausal women with lower-risk tumours who are not advised/recommended to receive OFS may benefit more from ChT

||The role of ChT is largely determined by tumour pathology including high-risk genomic signature scores (preferred) or high grade and/or high Ki-67 (> 30%)

¶Limited follow-up from a single study suggests that adjuvant abemaciclib may reduce recurrence in high-risk node-positive cancers characterised by stage, grade and/or Ki-67 (> 20%). In cases that are potential candidates for both abemaciclib and olaparib, olaparib is preferred due to greater and statistically significant OS benefit

*Adjuvant olaparib is indicated in BRCA1- or BRCA2-associated cancers with high-risk features that would typically warrant ChT, such as multiple positive LNs and/or residual disease after neoadjuvant ChT. In patients who are potential candidates for both abemaciclib and olaparib, olaparib is preferred due to greater and statistically significant OS benefit

††Use of AI in premenopausal women requires OFS

‡‡“Low risk” implies low-risk genomic score (preferred) and/or lower-risk features on traditional pathological analysis including lower-grade histology, robust ER and PgR expression and lower measures of proliferation. “High risk” implies high-risk genomic score and/or higher-risk features on traditional pathological analysis, including higher-grade histology, lower ER expression and higher measures of proliferation

§§There is no evidence of benefit for OFS beyond 5 years’ duration of therapy

AI, aromatase inhibitor; ChT, chemotherapy; EBC, early breast cancer; ER, oestrogen receptor; ET, endocrine therapy; gBRCA1/2, germline BRCA1/2; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LN, lymph node; m, mutation; N, node; OFS, ovarian function suppression; OS, overall survival; PgR, progesterone receptor; T, tumour; TN, tumour–node

Table adapted with permission from ST Gallen International Consensus Guidelines 2021

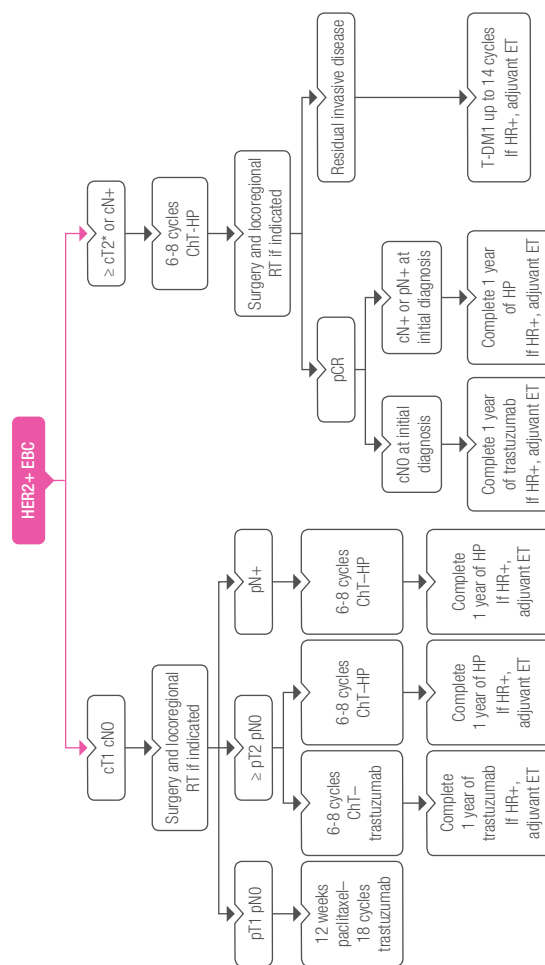
- In cases of uncertainty about indications for adjuvant ChT (after consideration of all clinical and pathological factors), gene expression assays or endocrine response assessment can be used to guide adjuvant ChT decisions
- Luminal B-like HR-positive, HER2-negative tumours should be treated with ChT followed by ET. ChT should be considered in cases of high clinical risk (e.g. multinode-positive, premenopausal node-positive, locally advanced) and 0-3 involved LNs with high-risk features (e.g. high-risk gene expression assay result)
- Anthracycline, taxane and alkylator-based ChT regimens are standard but non-anthracycline-based regimens may be appropriate for stage I and II cancers with limited nodal involvement
- Premenopausal women should receive either tamoxifen alone (luminal A like, stage I), or in case of a high risk of recurrence, ovarian suppression with either ovarian function suppression (OFS)–tamoxifen or OFS–aromatase inhibitor (AI)
- Postmenopausal women should receive an AI or tamoxifen followed by an AI
 - Tamoxifen can be given for lower-risk tumours or if AIs are not tolerated
- Bisphosphonates are recommended in women without ovarian function (postmenopausal women or those undergoing OFS), especially if they are at high risk of relapse or treatment-related bone loss, since they can lower the risk of tumour recurrence and mitigate the side-effects of osteopenia/osteoporosis seen with AIs

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

HER2-positive EBC

- Recommendations for the management of HER2-positive EBC are shown in the figure opposite
- HER2-directed therapy (with initial concurrent ChT) should be given for 12 months, covering both the neoadjuvant and/or adjuvant phases of treatment. Administration can be combined, if indicated, with RT and ET. In selected low-risk situations, 6 months of anti-HER2 therapy may be non-inferior
- Regular cardiac assessments are recommended prior to, during and after HER2-directed therapy with the option of additional assessments prior to the start of any ChT treatment
- For patients with clinical stage II-III HER2-positive breast cancer (e.g. T > 2 cm or node-positive), neoadjuvant systemic ChT with anti-HER2 therapy comprising trastuzumab-pertuzumab (HP) is the preferred option
- For the ChT backbone, a regimen of anthracycline-taxane or taxane-carboplatin is evidence-based, independent of neoadjuvant or adjuvant use
- Dual blockade with HP (versus trastuzumab alone) combined with ChT achieves higher pathological complete response (pCR) rates and is recommended for neoadjuvant therapy
- Patients with residual invasive disease (non-pCR after neoadjuvant ChT and anti-HER2 therapy) should receive adjuvant treatment with trastuzumab emtansine for up to 14 cycles
- For patients with stage I (T1a-b N0) HER2-positive EBC, primary surgery may be carried out followed by adjuvant paclitaxel for 12 weeks plus 1 year of trastuzumab if the clinical stage is confirmed by pathology
- For patients with pathological stage II or III cancer treated with initial surgery, adjuvant ChT combined with 1 year of anti-HER2 therapy should be given

MANAGEMENT OF HER2-POSITIVE EBC



*Tumours < 2cm can be considered for neoadjuvant therapy

c, clinical; ChT, chemotherapy; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HP, trastuzumab-pertuzumab; HR, hormone receptor; N, node; p, pathological; pCR, pathological complete response; RT, radiotherapy; T, tumour; T-DM1, trastuzumab emtansine

- In patients with node-positive disease, the addition of pertuzumab to trastuzumab should be strongly considered in the adjuvant setting irrespective of HR status
- Patients with high-risk HR-positive tumours may be considered for extended treatment with neratinib (concurrent with ET) for 1 year after completion of 1 year of trastuzumab

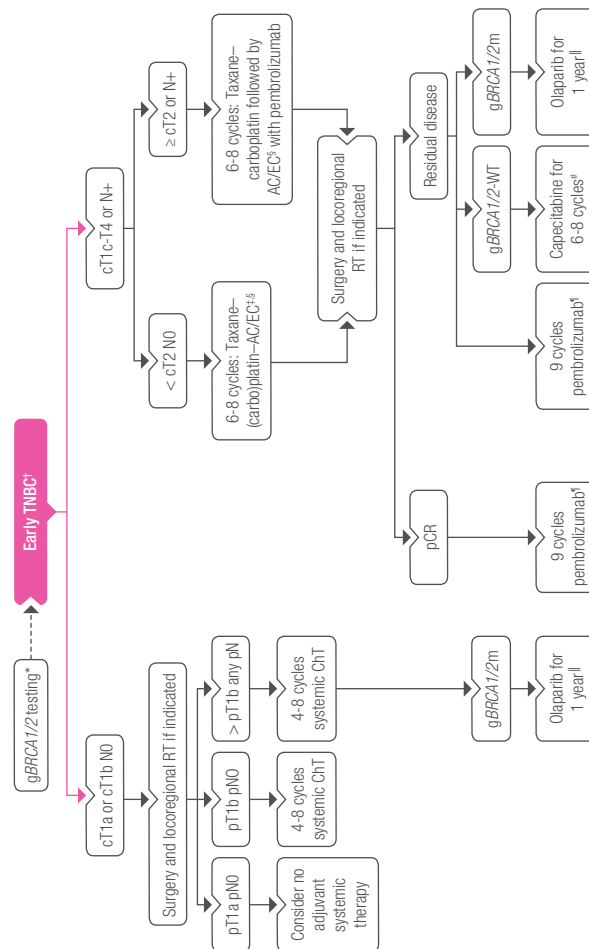
TNBC

- Recommendations for the management of early TNBC is shown in the figure opposite
- TNBC tumours should be treated with ChT with or without an immune checkpoint inhibitor (ICI) (pembrolizumab), except for some node-negative special histological subtypes such as secretory or adenoid cystic carcinomas or very low clinical risk [pathological (p)T1a pN0] tumours
- ChT should be administered for 12-24 weeks (four to eight cycles) depending on the stage of the disease and regardless of whether an ICI is added
- For cT1c-4 N0, or any N-positive TNBC, neoadjuvant treatment is preferred
- cT2-4 N0 or any N-positive (stage II-III) TNBC should be treated with neoadjuvant ChT plus pembrolizumab unless there are risk factors for excessive ICI-associated immune toxicity
- Pembrolizumab should be administered every 3 weeks throughout the neoadjuvant phase and for nine 3-week cycles during the adjuvant phase, regardless of pCR status
- Patients receiving pembrolizumab should be monitored very closely for the risk of immune-related adverse events throughout treatment and following the ESMO CPG for the management of toxicities from immunotherapy (<https://www.esmo.org/guidelines/guidelines-by-topic/supportive-and-palliative-care/toxicities-from-immunotherapy>)
- An ICI should not be given solely as adjuvant therapy without prior neoadjuvant ICI treatment
- In patients with gBRCA1/2m and high-risk TNBC (non-pCR or pathological stage II-III), 1 year of adjuvant olaparib should be administered
 - The combination of ICIs and olaparib may be considered on an individual basis
- Patients with residual disease who did not receive ICIs should be offered adjuvant capecitabine for six to eight cycles
 - The combination of olaparib and capecitabine in patients with gBRCAm should not be used
 - The combination of ICI and capecitabine may be considered on an individual basis

Special situations

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

MANAGEMENT OF EARLY TNBC



*See the ESMO CPG for risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes (<https://www.esmo.org/guidelines/guidelines-by-topic/hereditary-syndromes/risk-reduction-screening-hereditary-breast-ovarian-cancer-syndromes>)

*HER2-negative, HR-low tumours are a heterogeneous group, some of which behave biologically similarly to TNBC; therapeutic strategies should therefore be adjusted to this specific situation since this might lead to a higher response to ChT and reduced efficacy of ET compared with classical HR-positive breast cancer

*These evidence-based regimens without ICIs are sequential: Anthracycline-based therapy followed by a taxane or taxane–(carboplatin) or vice versa

*The use of dose-dense schedules of ChT, with G-CSF support, should be considered given their documented benefit over non-dose-dense schedules

*Olaparib is indicated as adjuvant therapy for patients with gBRCA1/2m tumours and non-pCR or ≥ pT2 or ≥ pN1 if treated with initial surgery

*Only if pembrolizumab was given preoperatively

*Only for ICI-naïve patients.

AC, doxorubicin–cyclophosphamide; c, clinical; ChT, chemotherapy; CPG, Clinical Practice Guideline; EC, epirubicin–cyclophosphamide; ESMO, European Society for Medical Oncology; ET, endocrine therapy; gBRCA1/2, germline BRCA1/2; G-CSF, granulocyte colony-stimulating factor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICI, immune checkpoint inhibitor; m, mutation; N, node; p, pathological; pCR, pathological complete response; RT, radiotherapy; T, tumour; TNBC, triple-negative breast cancer; WT, wild type

- A geriatric assessment should be carried out before making treatment decisions
- Tamoxifen is the standard adjuvant ET for male patients with breast cancer
- As with premenopausal women with breast cancer, a gonadotropin-releasing hormone agonist (GnRHa) may be added in higher-risk male patients with breast cancer, and a combination of AI–GnRHa should be considered in cases where tamoxifen is contraindicated
- An AI must be administered with a GnRHa when used as adjuvant ET in male patients with breast cancer
- In male patients with breast cancer, ChT, ET, anti-HER2, ICI, cyclin-dependent kinase 4/6 inhibitor and poly (ADP-ribose) polymerase inhibitor therapy indications and regimens should follow the same recommendations as those for breast cancer in female patients
- Ductal carcinoma *in situ* (DCIS) should be preferentially treated with BCS and whole-breast RT or, in cases of extensive or multicentric DCIS, mastectomy
- Both tamoxifen and AIs may be used after local breast-conserving therapy (BCT) for DCIS to prevent local recurrence and to decrease the risk of developing a second primary breast cancer
- Following mastectomy for DCIS, tamoxifen or AIs might be considered to decrease the risk of contralateral breast cancer in patients with a high risk of new breast tumours

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

General follow-up considerations

- The aims of follow-up are:
 - To detect local and/or regional recurrences or contralateral breast cancers that are potentially curable
 - To evaluate and treat therapy-related side-effects and complications
 - To promote adherence to adjuvant systemic treatment
 - To provide support to enable a return to normal life after breast cancer
 - To detect second primary cancers
- Regular follow-up visits are recommended every 3 months in the first 3 years post-treatment (every 6 months for low-risk EBC), every 6 months from years 4–5 and annually thereafter. The interval of visits can be adapted to the risk of relapse and patient needs
- Annual bilateral (after BCT) or contralateral mammography (after mastectomy) is recommended plus US and breast MRI, when needed
- Breast cancer survivors should participate in national screening programmes for other cancers
- In asymptomatic patients, laboratory tests (e.g. blood counts, routine chemistry, tumour marker assessment) or other imaging are not recommended
- Symptom-directed investigations should be considered as indicated
- Regular bone density evaluation is recommended for patients on AIs or undergoing OFS
- In asymptomatic patients with normal cardiac function who have received potentially cardiotoxic treatment, cardiac follow-up should be carried out as clinically indicated
- For patients on tamoxifen, an annual gynaecological examination is recommended; however, routine transvaginal US is not recommended

Long-term implications

- The number of survivors following treatment for an initial presentation of EBC is increasing and so the long-term effects of treatment must be recognised and monitored
- Notable potential long-term side-effects of adjuvant treatment for breast cancer are summarised in the table on the next page

NOTABLE POTENTIAL LONG-TERM SIDE-EFFECTS RELATED TO ADJUVANT BREAST CANCER TREATMENT*

CATEGORY	SIDE-EFFECT
Nervous system	Neurocognitive dysfunction
	Neuropathy
Musculoskeletal and connective tissue	Arthralgia
	Myalgia
Psychosocial	Chronic fatigue
	Emotional reactions to the diagnosis and treatment
	Exhaustion
	Sleep disturbances
Reproductive and sexual	Infertility
	Ovarian dysfunction
	Premature menopause
	Sexual complaints
Vascular disorders	Hot flushes
	Lymphoedema
Others	Bone density loss
	Cardiac dysfunction
	Chronic hair loss and thinning
	Dry mucosa (oral, genital, conjunctiva)
	Nutritional (e.g. weight gain)
	Secondary haematological malignancies (or other secondary cancers)

*Occurrences are rare and patients generally recover; quality of life in general recovers by end of therapy to that of before treatment start

Reproductive and sexual health considerations

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

Psychosocial considerations

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

GLOSSARY

AI, aromatase inhibitor
 ALN, axillary lymph node
 ALND, axillary lymph node dissection
 ATM, ATM serine/threonine kinase
BARF1, *BRCA1* associated ring domain 1
 BC, breast cancer
 BCS, breast-conserving surgery
 BCT, breast-conserving therapy
 BM, brain metastasis
 BMA, bone-modifying agent
 BRRM, bilateral risk-reducing mastectomy
 c, clinical
CDH1, cadherin 1
 CDK4/6, cyclin-dependent kinase 4 and 6
CHEK2, checkpoint kinase 2
 ChT, chemotherapy
 CNS, central nervous system
 CPG, Clinical Practice Guideline
 CPS, combined positive score
 CT, computed tomography
 DCIS, ductal carcinoma *in situ*
 DFI, disease-free interval
 EANO, European Association of Neuro-Oncology
 EBC, early breast cancer
 EMA, European Medicines Agency
 ER, oestrogen receptor
 ESMO, European Society for Medical Oncology
ESR1, oestrogen receptor 1
 ET, endocrine therapy
 FDA, Food and Drug Administration
 FDG, [¹⁸F]-fluoro-2-deoxy-D-glucose
 FNA, fine-needle aspiration
*gBRCA1/2*m, germline *BRCA1/2* mutation
 GnRH_a, gonadotropin-releasing hormone agonist
 HBOC, hereditary breast and ovarian cancer syndrome
 HER2, human epidermal growth factor receptor 2
 HP, trastuzumab–pertuzumab
 HR, hormone receptor
 ICI, immune checkpoint inhibitor
 IHC, immunohistochemistry
 LM, leptomeningeal metastasis
 LN, lymph node

LRT, locoregional treatment
 MBC, metastatic breast cancer
 MRI, magnetic resonance imaging
 MSCC, metastatic spinal cord compression
 MSI, microsatellite instability
 mTNBC, metastatic triple-negative breast cancer
 NSM, nipple-sparing mastectomy
NTK, neurotrophic tyrosine receptor kinase
 OFS, ovarian function suppression
 OMD, oligometastatic disease
 OS, overall survival
 p, pathological
PALB2, partner and localiser of *BRCA2*
 PARP, poly (ADP-ribose) polymerase
 pCR, pathological complete response
 PD, progressive disease
 PD-L1, programmed death-ligand 1
 PET, positron emission tomography
 PFS, progression-free survival
 PgR, progesterone receptor
 PGT, preimplantation genetic testing
PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
 PMRT, post-mastectomy radiotherapy
 PRO, patient-reported outcome
 PRS, polygenic risk score
 PST, primary systemic therapy
PTEN, phosphatase and tensin homologue
 PV, pathogenic variant
 QoL, quality of life
RAD51C, *RAD51* paralogue C
RAD51D, *RAD51* paralogue D
 RRBSO, risk-reducing bilateral salpingo-oophorectomy
 RRM, risk-reducing mastectomy
 RRMd, risk-reducing medication
 RT, radiotherapy
 SLN, sentinel lymph node
 SLNB, sentinel lymph node biopsy
 SNP, single nucleotide polymorphism
 SRE, skeletal-related event
 SRS, stereotactic radiosurgery
 SSM, skin-sparing mastectomy
STK11, serine/threonine kinase 11

GLOSSARY (CONT'D)

T-DM1, ado-trastuzumab emtansine

TIL, tumour-infiltrating lymphocyte

TKI, tyrosine kinase inhibitor

TM, total mastectomy

TNBC, triple-negative breast cancer

TNM, tumour–node–metastasis

TP53, tumour suppressor protein p53

UICC, Union for International Cancer Control

US, ultrasound

WBRT, whole brain radiotherapy

WHO, World Health Organization

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