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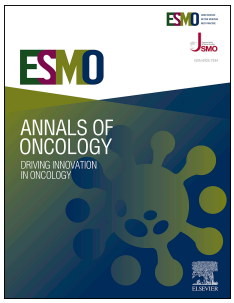

Metastatic breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up†

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

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Highlights (online only)

- This ESMO Clinical Practice Guideline provides key recommendations and algorithms for managing MBC.
- The guideline covers diagnosis, staging, risk assessment, treatment, disease monitoring and the patient perspective.
- The provided ESMO-MCBS scores, ESCAT scores and LoE/GoRs can aid with setting priorities.
- Treatment and management algorithms for advanced/metastatic and recurrent disease are provided.
- In clinical practice, all recommendations provided need to be discussed with patients in a shared decision-making approach.

INCIDENCE AND EPIDEMIOLOGY

Information on the incidence and epidemiology of breast cancer (BC) is provided in **Supplementary Material Section 1**.

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Details regarding the diagnosis, pathology and molecular biology of metastatic BC (MBC) are provided in **Supplementary Material Section 2**. An algorithm for the diagnostic work-up and staging of MBC is shown in **Figure 1**.

Recommendations

- At first diagnosis of MBC, a biopsy is recommended to confirm histology and re-assess tumour biology, if feasible {i.e. estrogen receptor [ER], progesterone receptor [PgR] and human epidermal growth factor receptor 2 [HER2] status [ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) score: I-A]} [I, A].
- In case of important differences in ER, PgR and HER2 status between the primary tumour and recurrence, patients can generally be managed according to the receptor status of the recurrent disease biopsy [V, B].
- Evaluation of programmed death-ligand 1 (PD-L1) status is recommended in triple-negative BC (TNBC) [I, A].
- Evaluation of germline *BRCA1/2* mutation status [ESCAT score: I-A] and germline *PALB2* mutation status [ESCAT score: II-B] is recommended in HER2-negative MBC if specific treatments are available [I, A]. Somatic *BRCA1/2* mutation status testing is also recommended in HER2-negative MBC if specific treatments are available [III, A; ESCAT score: II-B].
- Evaluation of *PIK3CA* mutations is recommended in ER-positive, HER2-negative MBC if phosphoinositide 3-kinase inhibitors are available [I, A; ESCAT score: I-A].
- Evaluation of *ESR1* mutations [circulating tumour DNA (ctDNA) or tumour tissue] is recommended in ER-positive, HER2-negative MBC following

progression on an aromatase inhibitor (AI) with or without a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor [I, A; ESCAT score: I-A].

- Evaluation of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) pathway alterations (*PIK3CA*, *PTEN* and *AKT1* mutations) using ctDNA or metastatic or primary tumour biopsies is recommended in ER-positive, HER2-negative MBC, mainly in the endocrine resistant setting, if specific treatments are available [I, A; ESCAT score: I-A].
- In patients who are not candidates for ET, reassessment of HER2 status by immunohistochemistry and/or *in situ* hybridisation (HER2-low, -ultralow or -0) is recommended [I, A; ESCAT score: I-A].
- Genomic profiling and further diagnostic tests (e.g. on tumour tissue or ctDNA) can be recommended for all patients if the result will change the treatment approach or if appropriate clinical trials are available [III, B].

STAGING AND RISK ASSESSMENT

Information on staging and risk assessment of MBC is provided in **Supplementary Material Section 3**.

Recommendations

- Computed tomography (CT) of the chest and abdomen and bone scintigraphy can be recommended as the minimum imaging work-up for baseline staging, as well as blood tests, including liver function tests [II, B].
- [^{18}F]2-fluoro-2-deoxy-D-glucose–positron emission tomography (PET)–CT can also be recommended [II, B].
- An interval of ≤4 weeks between baseline imaging and treatment initiation can be recommended [V, B].
- To ensure comparability, the imaging modality used at baseline can also be recommended for disease monitoring [III, B].
- Evaluation of response can be recommended every 2-4 months depending on patient symptoms, disease dynamics, location, extent of metastasis and type of treatment [V, B].

- Shortening of disease monitoring intervals cannot be recommended as there is no evidence of an overall survival benefit and there is potential for emotional and financial harm [IV, D].
- Less frequent monitoring can be recommended in certain cases, particularly for indolent disease and in later lines of treatment [V, B].
- If progression is suspected, additional tests should be carried out in a timely manner, irrespective of planned monitoring intervals [V, A].
- Repeat bone scans may be considered for bone-only and bone-predominant metastases, noting that interpretation may be confounded by a possible flare during the first few months of treatment [III, C].
- PET–CT may be considered to provide early guidance in monitoring treatment response outside the brain [III, C].
- CT or X-ray can be recommended for evaluation of impending fracture risk [V, B]. The spine instability neoplastic score may be considered for risk assessment for vertebral metastases [III, C].
- In case of suspected metastatic spinal cord compression (MSCC), magnetic resonance imaging (MRI) is recommended [I, A].
- Brain imaging cannot be recommended for asymptomatic patients at initial MBC diagnosis or during disease monitoring [V, D]. Subtype-oriented brain imaging may be considered in asymptomatic patients if detection of central nervous system metastases will alter the choice of systemic therapy, particularly in HER2-positive disease and TNBC [V, C].
- Brain imaging is recommended for symptomatic patients [II, A]. MRI can be recommended as the preferred technique [II, B].
- In case of suspicion of leptomeningeal disease (LMD), a lumbar puncture can be recommended for diagnosis [II, B].

GENERAL PRINCIPLES OF TREATMENT

Information on the general principles of treatment for MBC is provided in **Supplementary Material Section 4**.

MANAGEMENT OF LUMINAL MBC

Key recommendations regarding the management of luminal MBC are provided below. Supporting data for these recommendations are described in **Supplementary Material Section 5**.

Algorithms for the first-, second- and further-line management of patients with ER-positive, HER2-negative MBC are shown in **Figures 2, 3** and **4**.

Recommendations

First-line treatment

- Ovarian function suppression (OFS) or ovarian ablation is recommended in addition to all endocrine-based therapies in pre- and perimenopausal women [I, A].
- AI–CDK4/6 inhibitor is recommended for patients with ER-positive, HER2-negative MBC that is *de novo* or recurring >12 months after the end of adjuvant endocrine therapy (ET) [I, A]. Options include (in order of preference):
    - AI–ribociclib [ESMO-Magnitude of Clinical Benefit Scale (MCBS) v2.0 score: 4]
    - AI–abemaciclib (ESMO-MCBS v2.0 score: 1)
    - AI–palbociclib (ESMO-MCBS v2.0 score: 2).
- Fulvestrant–CDK4/6 inhibitor is recommended for patients with ER-positive, HER2-negative, *PIK3CA*-wild type MBC recurring while on adjuvant ET or ≤12 months after the end of adjuvant ET [I, A]. Options include:
    - Fulvestrant–palbociclib (ESMO-MCBS v2.0 score: 4)
    - Fulvestrant–ribociclib (ESMO-MCBS v2.0 score: 4)
    - Fulvestrant–abemaciclib (ESMO-MCBS v2.0 score: 3)
- For patients with ER-positive, HER2-negative, *PIK3CA*-mutated MBC recurring while on adjuvant ET or ≤12 months after the end of adjuvant ET:
    - Fulvestrant–palbociclib–inavolisib is recommended [I, A; ESMO-MCBS v2.0 score: 3].
    - Fulvestrant–CDK4/6 inhibitor can also be recommended [I, B]. Options include:

    - Fulvestrant–palbociclib (ESMO-MCBS v2.0 score: 4)
    - Fulvestrant–ribociclib (ESMO-MCBS v2.0 score: 4)
    - Fulvestrant–abemaciclib (ESMO-MCBS v2.0 score: 3)
- ET alone can be recommended for the small group of patients with comorbidities or a performance status that preclude the use of CDK4/6 inhibitor combinations [V, B].
- Chemotherapy (ChT) can be recommended for patients with imminent organ failure at MBC diagnosis [V, B].

Second-line treatment

- OFS or ovarian ablation is recommended in addition to all endocrine-based therapies in pre- and perimenopausal women [I, A].
- Selection of second-line therapy (endocrine or non-endocrine) based on disease aggressiveness, disease extent, organ function, progression-free survival on prior ET, somatic and germline mutational status and the associated toxicity profile, can be recommended [V, B].
- Fulvestrant–capivasertib is recommended for patients with tumours harbouring *PIK3CA*, *AKT1* or *PTEN* alterations who experience relapse or disease progression during or after treatment with an AI with or without previous CDK4/6 inhibitor therapy [I, A; ESMO-MCBS v2.0 score: 2].
- Fulvestrant–alpelisib can be recommended for patients with *PIK3CA*-mutated tumours (in exons 7, 9 or 20), prior exposure to an AI (with or without CDK4/6 inhibitors) and appropriate glycated haemoglobin levels [I, B; ESMO-MCBS v2.0 score: 1].
- Elacestrant [I, A; ESMO-MCBS v2.0 score: 3] or imlunestrant [I, A; ESMO-MCBS v2.0 score: 3] are recommended for patients with *ESR1*-mutated MBC after at least one line of ET, who preferably had a prolonged response to previous CDK4/6 inhibitor therapy.
- Poly (ADP-ribose) polymerase inhibitor (PARPi) monotherapy is recommended for patients with a germline *BRCA1/2* mutation [I, A].
    - Options include olaparib (ESMO-MCBS v2.0 score: 4) or talazoparib (ESMO-MCBS v2.0 score: 3).

- Olaparib or talazoparib can be recommended for patients with a germline *PALB2* mutation [II, B; not European Medicines Agency (EMA) or Food and Drug Administration (FDA) approved].
- For patients with tumours harbouring somatic pathogenic or likely pathogenic *BRCA1/2* mutations, PARPi monotherapy can also be recommended [II, B].
- Exemestane–everolimus [I, B; MCBS v2.0 score: 1], fulvestrant–everolimus [II, B; not EMA or FDA approved] or tamoxifen–everolimus [II, B; not EMA or FDA approved] can be recommended in the absence of targetable alterations in patients suitable for everolimus.
    - Steroid mouthwash is recommended for stomatitis prophylaxis in patients receiving everolimus [V, A].
- Fulvestrant–CDK4/6 inhibitor switch [II, C] or fulvestrant monotherapy (to a lesser extent) [I, C; MCBS v2.0 score: 1] may be considered in the absence of targetable alterations.

Third-line treatment and beyond

- At least two lines of endocrine-based therapy can be recommended before moving to non-endocrine-based therapy in endocrine-sensitive disease [V, B].
- For patients with endocrine-sensitive tumours, continuation of ET with agents not previously received in the metastatic setting can be recommended [III, B].
- ChT or antibody–drug conjugates (ADCs) can be recommended for patients with tumours considered endocrine resistant or refractory when targeted agents have already been used or ruled out due to lack of therapeutically relevant molecular alterations [V, B].
- For patients who have not previously received ChT:
    - ChT can be recommended [I, B].
        - Sequential single-agent ChT is recommended over combination strategies [II, A].
        - Combination ChT is recommended when a rapid response is needed due to imminent organ failure [V, A].

- Capecitabine, capecitabine–bevacizumab (not EMA or FDA approved in this line), taxane or taxane–bevacizumab (not EMA or FDA approved in this line), may be considered [I, C].
  - If capecitabine is used, dihydropyrimidine dehydrogenase testing is recommended before treatment is initiated [V, A].
- Trastuzumab deruxtecan (T-DXd) may be considered for patients with HER2-low or -ultralow disease after ≥2 lines of ET for MBC (or after one line of ET if progression occurred within 24 months of adjuvant ET or within 6 months of ET–CDK4/6 inhibitor for MBC) [I, C; MCBS v2.0 score: 3].

- For patients who have previously received ChT:
  - Sacituzumab govitecan can be recommended for patients with ER-positive, HER2-negative MBC after ≥1 line of ChT [I, B; ESMO-MCBS v2.0 score: 4].
  - Datopotamab deruxtecan (dato-DXd) can also be recommended for patients with ER-positive, HER2-negative MBC who have received ≥1 prior line of ChT [I, B; ESMO-MCBS v2.0 score: 3].
  - T-DXd is recommended for patients with HER2-low MBC after ≥1 line of ChT if not already used [I, A; ESMO-MCBS v2.0 score: 4].
  - Rechallenge with anthracyclines or taxanes (liposomal anthracyclines or protein-bound paclitaxel, if available) can be recommended beyond third-line treatment in patients with a disease-free interval (DFI) of ≥12 months [II, B].
- The optimal sequence of therapy in ER-positive MBC has not been established. Available options should be discussed with the patient [I, A].

MANAGEMENT OF HER2-POSITIVE MBC

Key recommendations regarding the management of HER2-positive MBC are provided below. Supporting data for these recommendations are described in **Supplementary Material Section 6**.

Algorithms for the first-, second- and further-line management of patients with HER-positive MBC are shown in **Figures 5, 6** and **7**.

Recommendations

First-line treatment

- Docetaxel–pertuzumab–trastuzumab is recommended for patients with HER2-positive MBC, regardless of ER status [I, A; ESMO-MCBS v2.0 score: 4].
    - Docetaxel should be administered for at least six cycles, if tolerated [I, A].
    - If required, an alternative taxane (paclitaxel, nab-paclitaxel) [II, A] or vinorelbine [III, A] are recommended as substitutes for docetaxel.
- T-DXd–pertuzumab is also recommended for patients with HER2-positive MBC, regardless of ER status [I, A; ESMO-MCBS v2.0 score: 2; FDA approved, not EMA approved].
- After completion of induction docetaxel–pertuzumab–trastuzumab:
    - Maintenance pertuzumab–trastuzumab–ET–palbociclib may be considered for HER2-positive, ER-positive tumours (preferred) [I, C; not EMA or FDA approved].
    - Maintenance pertuzumab–trastuzumab–ET is recommended for HER2-positive, ER-positive tumours [I, A; not EMA or FDA approved].
    - Maintenance pertuzumab–trastuzumab–tucatinib is recommended, regardless of ER status [I, A; not EMA or FDA approved].
    - Maintenance pertuzumab–trastuzumab is recommended for HER2-positive, ER-negative tumours [I, A; MCBS v2.0 score: 4].
- If ChT is contraindicated:
    - ET (e.g. an AI) can be recommended in combination with a HER2-targeted therapy such as trastuzumab [II, B; ESMO-MCBS v2.0 score: 3; EMA approved, not FDA approved], pertuzumab–trastuzumab [II, B; not EMA or FDA approved], lapatinib–trastuzumab [II, C; not EMA or FDA approved] or lapatinib [II, C; ESMO-MCBS v2.0 score: 3] for selected patients with HER2-positive, ER-positive MBC.
    - Single-agent ET may be considered in HER2-positive, ER-positive MBC if comorbidities (e.g. cardiac disease) preclude the safe use of HER2-directed therapies [III, C].

    - HER2-targeted therapy without ChT [e.g. pertuzumab–trastuzumab (not FDA or EMA approved) or trastuzumab monotherapy (not FDA or EMA approved)] may be considered in patients with HER2-positive, ER-negative MBC [III, C].
    - If taxane ChT is contraindicated, a less toxic ChT partner (e.g. capecitabine or vinorelbine) may be considered [III, C].
- OFS or ovarian ablation is recommended for pre- and perimenopausal women with ER-positive disease [I, A].
- Second-line therapy options can be recommended for patients with metastatic recurrence within 6-12 months of completing adjuvant pertuzumab–trastuzumab or trastuzumab emtansine (T-DM1) [II, B].

Second-line treatment

- T-DXd is recommended (preferred option when available) after progression on taxane–trastuzumab irrespective of the presence of brain metastases (BMs), if not used in the first line [I, A; ESMO-MCBS v2.0 score: 4].
- Tucatinib–trastuzumab–capecitabine is also recommended in the second line [I, A; ESMO-MCBS v2.0 score: 4 for overall population, 3 for patients with BMs; FDA approved, not EMA approved in second line].
- T-DM1 is recommended after progression on taxane–trastuzumab if T-DXd is not available [I, A; ESMO-MCBS v2.0 score: 3].
- For patients who experience intracranial progression without extracranial progression, local treatment of BMs and continuation of the same anti-HER2 treatment can be recommended [IV, B].

Third-line treatment

- T-DXd [II, A; ESMO-MCBS v2.0 score: 4], tucatinib–trastuzumab–capecitabine [I, A; ESMO-MCBS v2.0 score: 4 for overall population, 3 for patients with BMs] and T-DM1 [I, A; ESMO-MCBS v2.0 score: 3] are recommended options in the third-line setting, if not already used.

- For patients who experience intracranial progression without extracranial progression, local treatment of BMs and continuation of the same anti-HER2 treatment can be recommended [IV, B].

Fourth-line treatment and beyond

- T-DM1 is a recommended fourth-line option, if not already used [I, A; ESMO-MCBS v2.0 score: 3].
- Lapatinib–trastuzumab (ESMO-MCBS v2.0 score: 4; EMA approved, not FDA approved), lapatinib–capecitabine (ESMO-MCBS v2.0 score: 2) or lapatinib–ET (if ER positive; ESMO-MCBS v2.0 score: 3) may be considered in later lines of therapy [I, C], noting that no data are available on the use of lapatinib after tucatinib-based therapy.
- Margetuximab–ChT (ESMO-MCBS v2.0 score: 2; FDA approved, not EMA approved) or neratinib–capecitabine (ESMO-MCBS v2.0 score: 1; FDA approved, not EMA approved) may be considered in later lines of therapy [I, C].
    - In the absence of comparative data, the most appropriate setting may be when all standard therapy options have been exhausted [V, C], noting that there is no evidence for sequencing a tyrosine kinase inhibitor (TKI) after a prior TKI in HER2-positive MBC.
- Trastuzumab in combination with a ChT or ET agent that has not been used previously is recommended beyond progression when other anti-HER2 therapies have been exhausted, are not considered suitable or are not available [III, A].

MANAGEMENT OF METASTATIC TNBC

Key recommendations regarding the management of metastatic TNBC (mTNBC) are provided below. Supporting data for these recommendations are described in **Supplementary Material Section 7** and **Supplementary Table S1.**

Algorithms for the first-, second- and further-line management of patients with mTNBC are shown in **Figures 8** and **9**.

Recommendations

First-line treatment

- Immune checkpoint inhibitor (ICI)–ChT is the preferred option for patients with PD-L1-positive mTNBC:
    - Pembrolizumab–sacituzumab govitecan is recommended for patients with PD-L1 combined positive score (CPS) ≥10 and DFI ≥6 months after adjuvant treatment, noting that limited data are available after neo(adjuvant) ICI therapy [I, A; not EMA or FDA approved].
    - Pembrolizumab–ChT (paclitaxel, nab-paclitaxel or carboplatin–gemcitabine) is also recommended for patients with PD-L1 CPS ≥10 and DFI ≥6 months after adjuvant treatment, noting that limited data are available after neo(adjuvant) ICI therapy [I, A; ESMO-MCBS v2.0 score: 4].
    - Atezolizumab–nab-paclitaxel is recommended for patients with immune cell PD-L1 positivity ≥1% and DFI ≥12 months after adjuvant treatment [II, A; ESMO-MCBS v2.0 score: 3; EMA approved, not FDA approved].
- Olaparib [I, A; not EMA or FDA approved in first line], talazoparib [I, A; not EMA or FDA approved in first line] or carboplatin-based ChT [II, A] are recommended for patients with germline *BRCA1/2*-mutated and PD-L1-negative mTNBC.
- Treatment options for patients with germline *BRCA1/2*-wild type and PD-L1-negative mTNBC (or who are not candidates for ICIs) depend on previous treatment exposure, disease presentation, DFI and patient considerations:
    - Dato-DXd [I, A; not FDA or EMA approved] or sacituzumab govitecan [I, A; not FDA or EMA approved] are recommended for most patients, if available. Dato-DXd is the preferred option for patients relapsing within 6 months of adjuvant therapy [I, A].
    - Taxane monotherapy is recommended for most patients [I, A].
    - Anthracycline monotherapy is recommended in patients with no prior exposure or if rechallenge is possible [I, A].

- Capecitabine, capecitabine–bevacizumab (ESMO-MCBS v2.0 score: 3; EMA approved, not FDA approved), taxane or taxane–bevacizumab (ESMO-MCBS v2.0 score: 2; EMA approved, not FDA approved) can be recommended for patients with imminent organ failure [I, B].

Second-line treatment and beyond

- For patients with germline *BRCA1/2*-wild type mTNBC:
  - Sacituzumab govitecan is the preferred recommended option if not used in the first line [I, A; ESMO-MCBS v2.0 score: 5].
  - All ChT recommendations for HER2-negative disease can also be recommended for mTNBC, such as eribulin (ESMO-MCBS v2.0 score: 2), capecitabine and vinorelbine [I, B].
- For patients with a germline *BRCA1/2* mutation or a germline *PALB2* mutation:
  - Olaparib (ESMO-MCBS v2.0 score: 4) or talazoparib (ESMO-MCBS v2.0 score: 3) are recommended if a PARPi was not given in the first-line setting [I, A].
  - Carboplatin-based ChT is also recommended [II, A].
- After progression, sacituzumab govitecan is recommended for third-line treatment of mTNBC if not used previously [I, A; ESMO-MCBS v2.0 score: 5].
- All ChT recommendations for HER2-negative disease can also be recommended for third-line treatment of mTNBC, such as eribulin (ESMO-MCBS v2.0 score: 2), capecitabine and vinorelbine [I, B].
- T-DXd can be recommended as a third-line option in patients with HER2-low mTNBC [II, B; ESMO-MCBS v2.0 score: 4].

SITE-SPECIFIC MANAGEMENT

Details regarding the management of primary (*de novo*) stage IV BC, oligometastatic disease (OMD), bone metastases, BMs and leptomeningeal metastases (LMs) can be found in **Supplementary Material Section 8**. An algorithm for the site-specific management of OMD is shown in **Figure 10**.

Recommendations

Primary (*de novo*) stage IV BC

- Multidisciplinary team (MDT) discussion of therapeutic decisions can be recommended for patients with newly diagnosed stage IV BC and an intact primary tumour [II, B].
- Locoregional therapy (LRT) of the primary tumour in the absence of symptomatic local disease cannot be recommended [II, D].
- Consideration of LRT is recommended for patients with local symptoms caused by the primary tumour or metastatic disease [II, A].
- Surgical removal of the primary tumour can be considered according to patient preference and after MDT discussion [V, C].

OMD

- MDT discussion of cases can be recommended to individualise optimal management [V, B].
- Multimodality treatment approaches involving local or regional therapies [e.g. high conformal radiotherapy (RT), image-guided ablation and/or surgery] combined with systemic treatments can be recommended and should generally be tailored to the disease presentation in any individual patient [V, B].
- Systemic treatment can be recommended as the initial therapy for OMD, and further management decisions should generally be based on the initial response obtained [V, B].
- Ablative procedures may be considered on a case-by-case basis for individual metastatic lesions following MDT discussion [II, C].

Bone metastases and bone-modifying agents

- A multidisciplinary approach is recommended to manage patients with bone metastases and to prevent skeletal-related events (SREs) [V, A].

- An orthopaedic evaluation is recommended in case of significant lesions in long bones or vertebrae, as well as in patients with MSCC, to discuss the possible role of surgery [IV, A].
- RT is recommended for lesions at moderate risk of fracture and those associated with moderate to severe pain [I, A].
- A single 8 Gy RT fraction is recommended for uncomplicated bone metastases [I, A].
- RT can be recommended after stabilisation or separation surgery for MSCC [III, B].
- Bone-modifying agents (BMAs) such as bisphosphonates or denosumab are recommended for patients with bone metastases, regardless of symptoms [I, A].
    - Denosumab every 4 weeks is recommended and is more effective than zoledronic acid in delaying first and subsequent SREs [I, A].
    - Zoledronic acid every 12 weeks can be recommended for patients with stable disease after a ≥9-month treatment period [I, B].
- A thorough dental evaluation and completion of any required dental treatment are recommended before BMA initiation [III, A]. Calcium and vitamin D supplements are recommended [III, A].
- The optimal duration of BMA therapy has not been defined, but interruption of therapy after 2 years can be recommended for patients in remission [II, B].
- The ideal sequence of therapies has not been defined, but evaluation of tumour response to systemic treatment may be considered before suggesting LRT [V, C].

BMs

- The disease-specific graded prognostic assessment (DS-GPA) encompassing BC subtypes, age, disease progression, extracranial disease status and number of BMs is recommended to assess prognosis [III, A].
- Treatment decisions should consider DS-GPA, presence of neurological symptoms, previous treatments and the patient's preferences [V, A].
- Individual assessment by an MDT is recommended [V, A].

- BMs should be managed according to 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 [V, A].

LRT for BMs

- Stereotactic RT (SRT) is recommended over whole-brain RT [I, A].
- Simultaneous administration of SRT and ADCs cannot be recommended [IV, D].
- Reassessment of disease subtype in resected BMs is recommended [IV, A].
- Continuation of ongoing systemic therapy without modification is recommended following SRT in the absence of extracranial disease progression [III, A].

HER2-positive BC with BMs

- T-DXd is recommended as the preferred second-line option for HER2-positive BC with BMs [III, A; not EMA or FDA approved in this specific setting].
- If T-DXd is not available or not indicated, tucatinib–trastuzumab–capecitabine is recommended [II, A; MCBS v2.0 score: 3; FDA approved, not EMA approved in this specific setting].
- T-DM1 can also be recommended [III, B; not EMA or FDA approved in this specific setting].
- Tucatinib–trastuzumab–capecitabine is recommended for patients progressing on T-DXd [I, A; MCBS v2.0 score: 3]. If tucatinib is not available, lapatinib–capecitabine or neratinib–capecitabine can be recommended [III, B; neither of these regimens are EMA or FDA approved in this specific setting].
- Following progression, neratinib–trastuzumab–fulvestrant (in ER-positive disease), tucatinib or T-DXd can be recommended in *HER2*-mutated MBC with BMs [V, B; none of these regimens are EMA or FDA approved in this specific setting].

ER-positive BC and TNBC with BMs

- Local therapies are recommended for patients with HER2-negative BC and BMs [V, A].
- ChT can be recommended for HER2-negative BC BMs [III, B].
- Clinical decisions on ChT should be based on disease subtype, previous treatments, patients' general condition and individual preferences, as no single regimen is preferred [V, A].
- T-DXd is recommended for HER2-low expressing BC with active BMs [III, A; not EMA or FDA approved in this specific setting].
- PARPi is recommended over conventional ChT for patients with germline *BRCA1/2*-mutated MBC, irrespective of stable BMs [I, A].
- Bevacizumab (not EMA or FDA approved) is recommended in patients with BMs or radiation necrosis [II, A].

LMD

- LMD should be treated according to the recommendations outlined in the EANO–ESMO CPG for the management of patients with LMs from solid tumours [V, A].
- All treatment decisions should consider patients' general condition and preferences, disease subtype and LMD type [V, A].
- Hypofractionated involved-field RT or SRT is recommended in nodular disease or in case of symptomatic sites and is preferred over photon cerebrospinal RT [V, A].
- Intrathecal therapy may be considered in type I LMD (positive cytology or biopsy) after MDT discussion [III, C].
- In case of newly diagnosed LMD, a switch of systemic treatment is recommended in addition to RT and/or intrathecal therapy [V, A].
- T-DXd and tucatinib–trastuzumab–capecitabine are recommended as systemic treatment options in HER2-positive LMD [III, A; neither of these regimens is EMA or FDA approved in this specific setting].
- T-DXd can be recommended in case of HER2-low expressing LMD [III, B; not EMA or FDA approved in this specific setting].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Information on follow-up, long-term implications and survivorship for patients with MBC is provided in **Supplementary Material Section 9**.

Recommendations

- A multidisciplinary approach is recommended, including specialised oncology nurses to proactively identify and manage individual needs and treatment-emergent toxicities [I, A].
- Patients should receive thorough information regarding treatment options and potential side-effects, and all treatment plans should include comprehensive patient education on side-effect management [I, A].
- Side-effects should be carefully assessed at each visit and electronic patient-reported outcomes are recommended to facilitate this process [I, A].
- Quality of life (QoL) assessments should be incorporated into treatment efficacy evaluations [I, A].
- Dose reduction or treatment delays are recommended for managing toxicity [I, A].
- Proactive symptom management and education are recommended to improve QoL and reduce side-effects [I, A]. Supportive care should be holistic and should include sexual health and management of genitourinary symptoms [I, A].
- Counselling on the impact of treatment on fertility and fertility preservation options can be recommended for women of reproductive age, within the context of metastatic disease, the need for uninterrupted oncological care and prognosis [V, B].
- Women of reproductive age should be counselled about safe and effective contraception [I, A].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/guidelines/esmo-guidelines-methodology). All recommendations provided are based on current

scientific evidence and the authors' collective expert opinion. Where recommendations for multiple different treatment options exist, prioritisation is illustrated by ordering these options according to: level of evidence (LoE) and grade of recommendation (GoR); where equal, by ESMO-MCBS score; where equal, by alphabetical order. The relevant literature has been selected by the expert authors. ESCAT scores have been defined by the authors, assisted if needed by the ESMO Precision Oncology Task Force.[1] ESMO-MCBS v2.0[2] was used to calculate scores for new therapies/indications approved by the EMA or FDA (https://www.esmo.org/guidelines/esmo-mcbs). The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors. The ESMO-MCBS scores and corresponding scorecard links included in this CPG are correct at the time of publication. For the most up-to-date scores, please refer to the scorecards linked in **Supplementary Table S2**. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. LoEs and GoRs have been applied using the system shown in **Supplementary Table S3**.[3] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including Express Updates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/esmo-clinical-practice-guideline-metastatic-breast-cancer.

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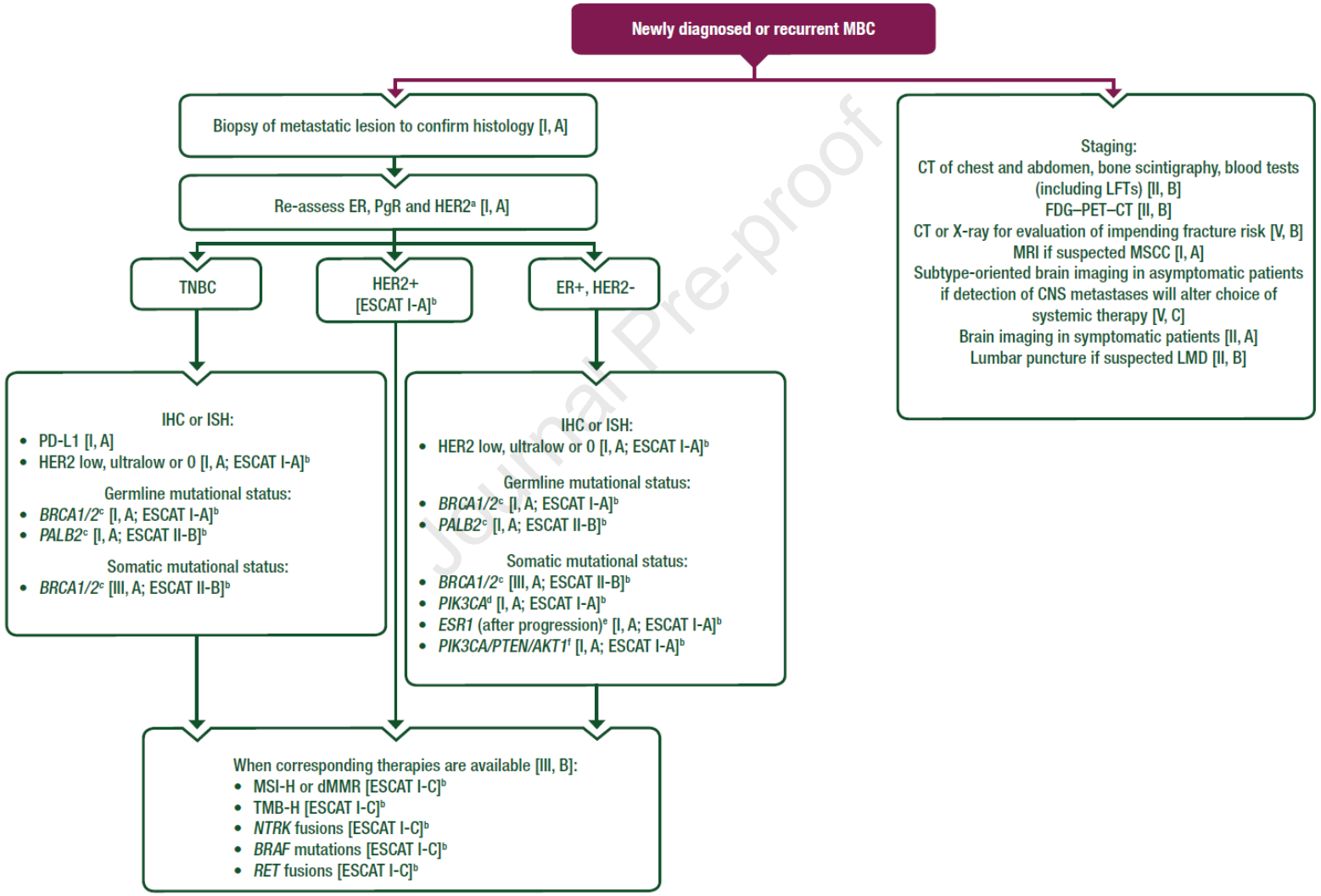
1. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol.* 2018;29(9):1895-1902.
2. Cherny NI, Oosting SF, Dafni U, et al. ESMO-Magnitude of Clinical Benefit Scale version 2.0 (ESMO-MCBS v2.0). *Ann Oncol.* 2025;36(8):866-908.
3. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2001;33(2):139-144 [adapted from: Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. *Clin Infect Dis*. 1994;18(3):421].

FIGURES

Figure 1. Diagnostic work-up and staging for MBC.



Purple: algorithm title; white: other aspects of management and non-treatment aspects.

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4 and 6; CNS, central nervous system; CT, computed tomography; dMMR, mismatch repair deficient; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDG, [^{18}F]2-fluoro-2-deoxy-D-glucose; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridisation; LFT, liver function test; LMD, leptomeningeal disease; MBC, metastatic breast cancer; MRI, magnetic resonance imaging; MSCC, metastatic spinal cord compression; MSI-H, microsatellite instability high; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PgR, progesterone receptor; TMB-H, tumour mutation burden high; TNBC, triple-negative breast cancer.

[a]In case of important differences in ER, PgR and HER2 status between the primary tumour and recurrence, patients can be managed according to the receptor status of the recurrent disease biopsy [V, B].

[b]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors, assisted if needed by the ESMO Precision Oncology Task Force.[1]

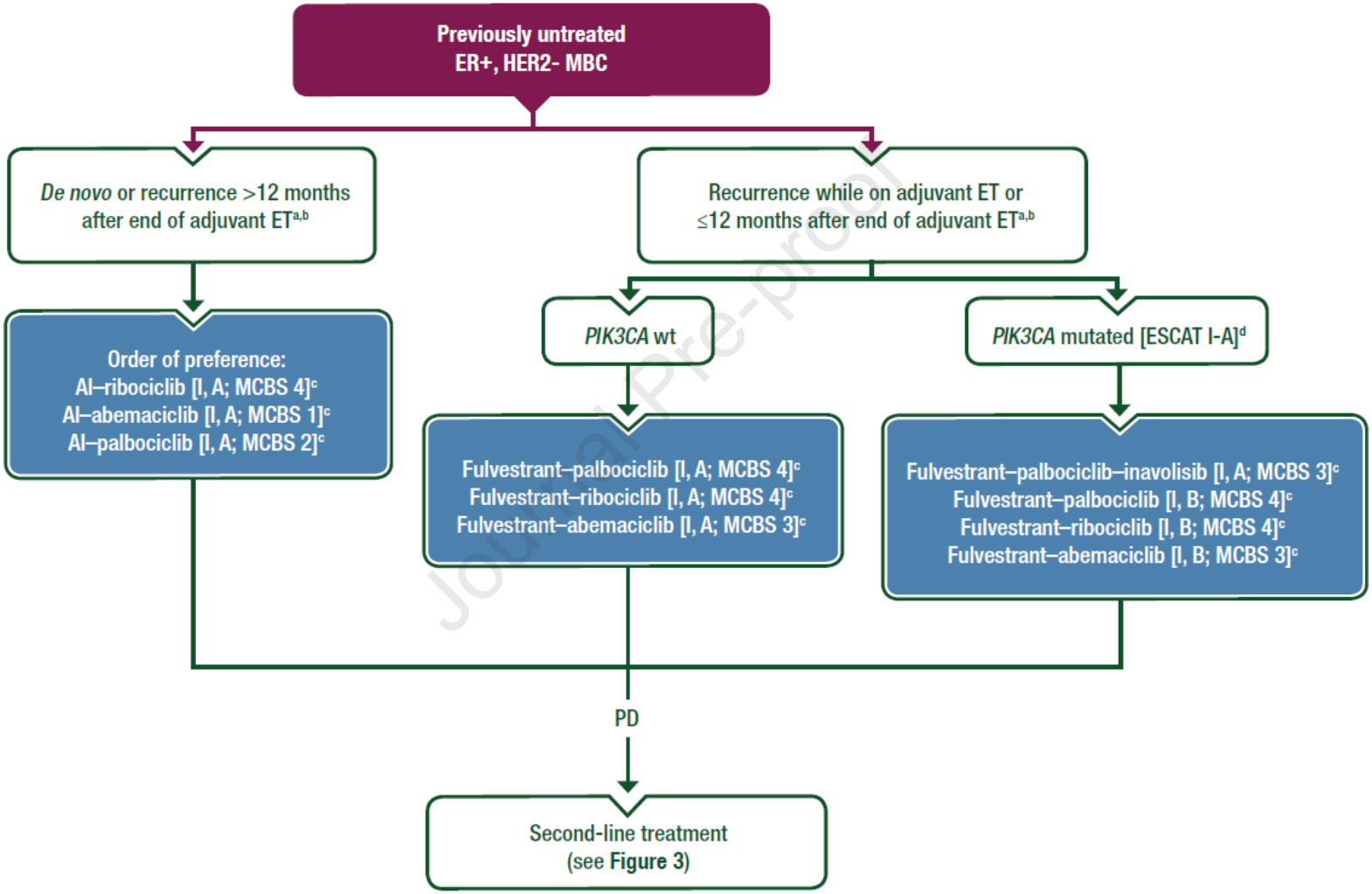
[c]If specific treatments are available.

[d]If phosphoinositide 3-kinase inhibitors are available.

[e]Following progression on an AI with or without a CDK4/6 inhibitor.

[f]Mainly in the endocrine resistant setting, if specific treatments are available.

Figure 2. First-line management of ER-positive, HER2-negative MBC.



Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4 and 6; ChT, chemotherapy; EMA, European Medicines Agency; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; MCBS, Magnitude of Clinical Benefit Scale; PD, progressive disease; PS, performance status; wt, wild type.

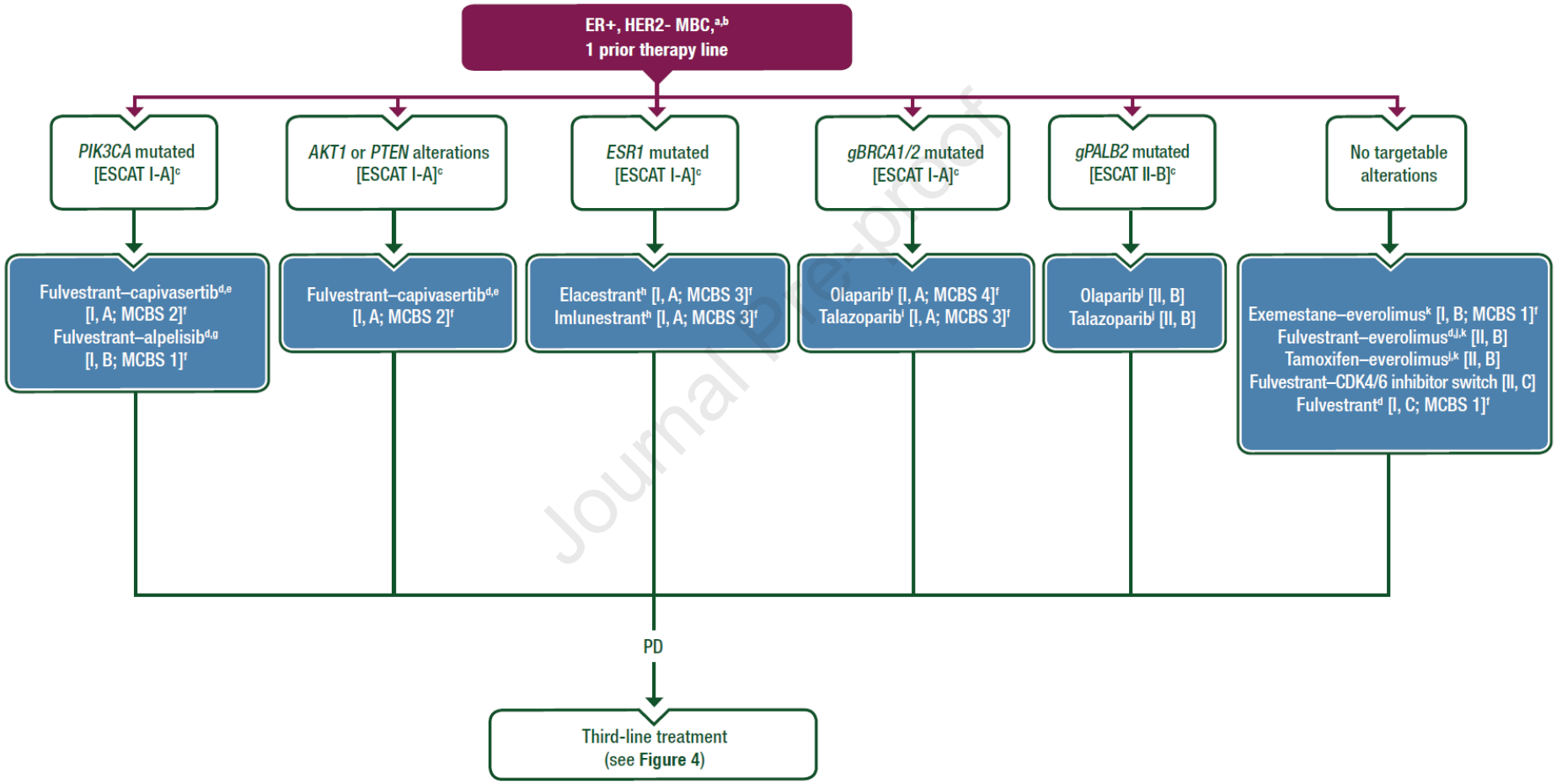
[a]ET alone can be recommended for the small group of patients with comorbidities or a PS that precludes the use of CDK4/6 inhibitor combinations [V, B]. ChT can be recommended for patients with imminent organ failure at MBC diagnosis [V, B].

[b]Ovarian function suppression or ovarian ablation is recommended in addition to all endocrine-based therapies in pre- and perimenopausal women [I, A].

[c]ESMO-MCBS v2.0[2] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[d]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors, assisted if needed by the ESMO Precision Oncology Task Force.[1]

Figure 3. Second-line management of ER-positive, HER2-negative MBC.



Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4 and 6; EMA, European Medicines Agency; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ET, endocrine therapy; FDA, Food and Drug Administration; g, germline; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; MCBS, Magnitude of Clinical Benefit Scale; PARPi, poly (ADP-ribose) polymerase inhibitor; PD, progressive disease.

[a]Selection of second-line therapy (endocrine or non-endocrine) based on disease aggressiveness, disease extent, organ function, progression-free survival on prior ET, somatic and germline mutational status and the associated toxicity profile, can be recommended [V, B].

[b]Ovarian function suppression or ovarian ablation is recommended in addition to all endocrine-based therapies in pre- and perimenopausal women [I, A].

[c]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors, assisted if needed by the ESMO Precision Oncology Task Force.[1]

[d]If not previously exposed to fulvestrant.

[e]Patients experiencing relapse or PD during or after treatment with an AI with or without previous CDK4/6 inhibitor therapy.

[f]ESMO-MCBS v2.0[2] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[g]Patients with *PIK3CA*-mutated tumours (in exons 7, 9 or 20), prior exposure to an AI (with or without CDK4/6 inhibitors) and appropriate glycated haemoglobin levels.

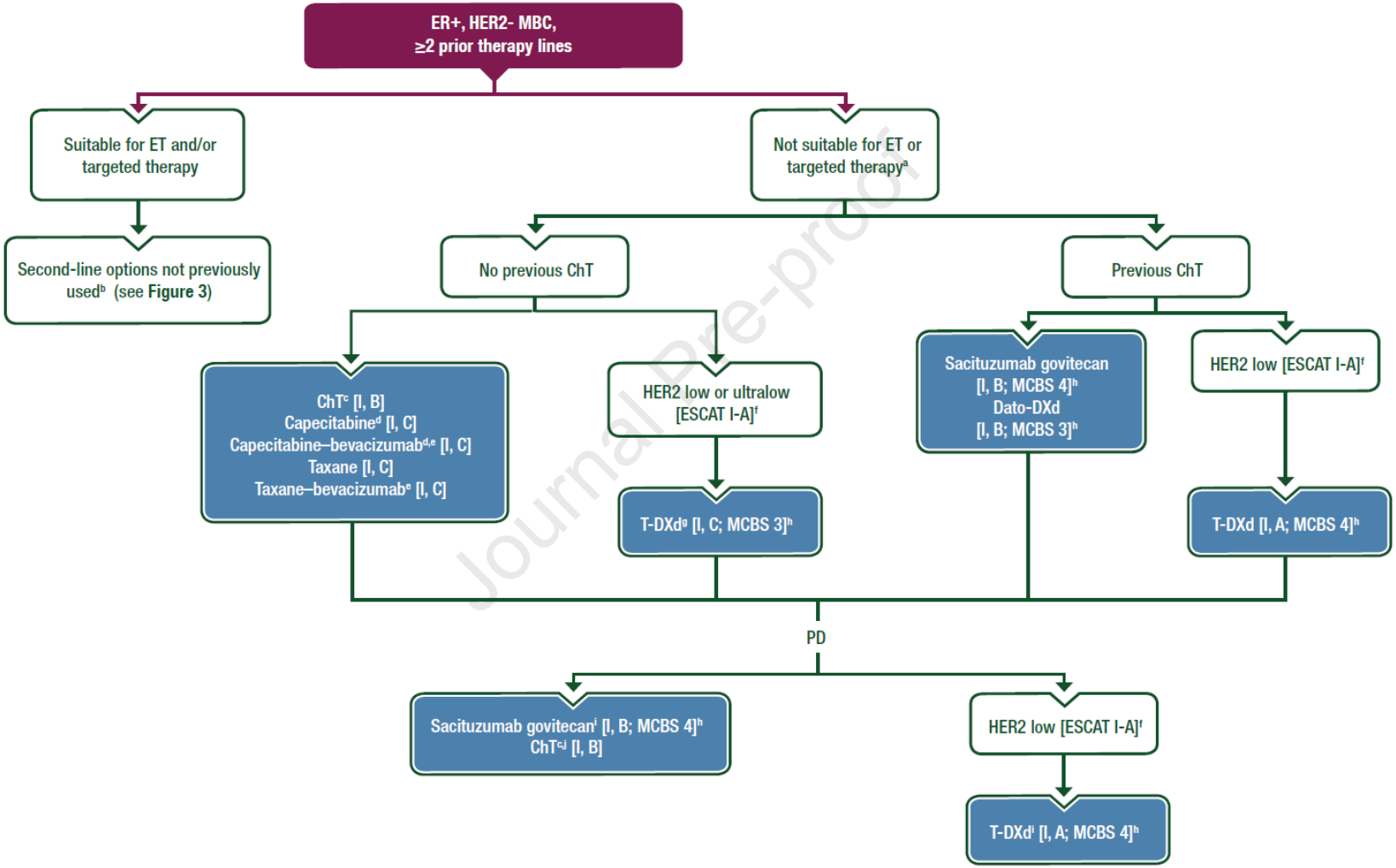
[h]After at least one line of ET, preferably in patients who had a prolonged response to previous CDK4/6 inhibitor therapy.

[i]For patients with tumours harbouring somatic pathogenic or likely pathogenic *BRCA1/2* mutations, PARPi monotherapy can also be recommended [II, B; ESCAT score: II-B].

[j]Not EMA or FDA approved.

[k]Steroid mouthwash is recommended for stomatitis prophylaxis in patients receiving everolimus [V, A].

Figure 4. Third- and further-line management of ER-positive, HER2-negative MBC.



Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.

ADC, antibody–drug conjugate; CDK4/6, cyclin-dependent kinase 4 and 6; ChT, chemotherapy; dato-DXd, datopotamab deruxtecan; EMA, European Medicines Agency; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; MCBS, Magnitude of Clinical Benefit Scale; PD, progressive disease; T-DXd, trastuzumab deruxtecan.

[a]ChT or ADCs can be recommended for patients with tumours considered endocrine resistant when targeted agents have already been used or ruled out due to lack of therapeutically relevant molecular alterations [V, B].

[b]At least two lines of endocrine-based therapy can be recommended before moving to non-endocrine-based therapy [V, B]. For patients with endocrine-sensitive tumours, continuation of ET with agents not previously received in the metastatic setting can be recommended [III, B].

[c]Sequential single-agent ChT is recommended over combination strategies [II, A]. Combination ChT is recommended when a rapid response is needed due to imminent organ failure [V, A].

[d]If capecitabine is used, dihydropyrimidine dehydrogenase testing is recommended before treatment is initiated [V, A].

[e]Not EMA or FDA approved in this line.

[f]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors, assisted if needed by the ESMO Precision Oncology Task Force.[1]

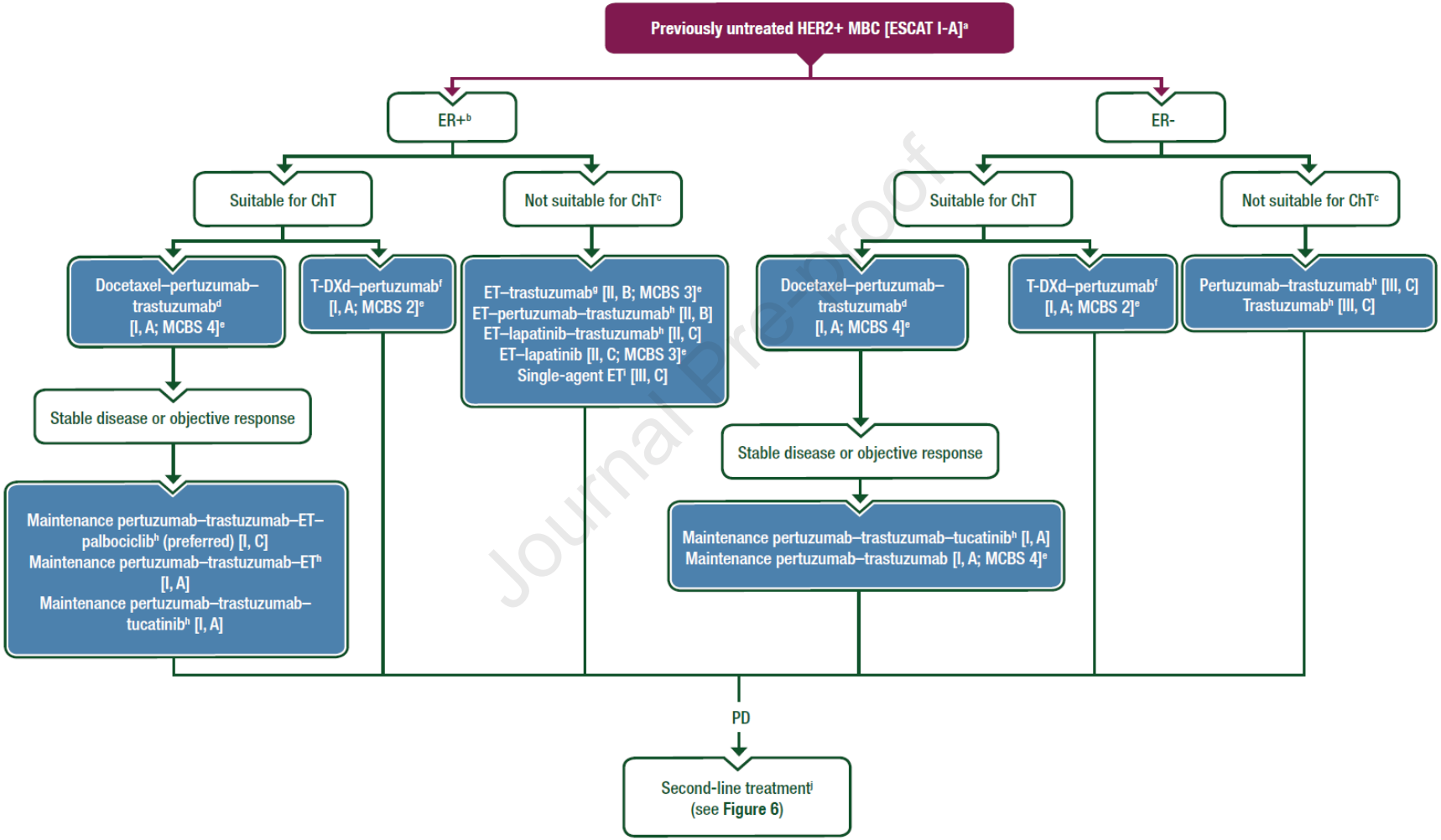
[g]After ≥2 lines of ET for MBC, or after one line of ET if progression occurred within 24 months of adjuvant ET or within 6 months of ET–CDK4/6 inhibitor for MBC.

[h]ESMO-MCBS v2.0[2] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[i]If not used previously.

[j]Rechallenge with anthracyclines or taxanes (liposomal anthracyclines or protein-bound paclitaxel, if available) can be recommended in patients with a disease-free interval of ≥12 months [II, B].

Figure 5. First-line management of HER2-positive MBC.



Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.

ChT, chemotherapy; EMA, European Medicines Agency; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; MCBS, Magnitude of Clinical Benefit Scale; PD, progressive disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors, assisted if needed by the ESMO Precision Oncology Task Force.[1]

[b]Ovarian function suppression or ovarian ablation is recommended for pre- and perimenopausal women [I, A].

[c]If taxane ChT is contraindicated, a less toxic ChT partner (e.g. capecitabine or vinorelbine) may be considered [III, C].

[d]Docetaxel should be administered for ≥6 cycles [I, A]. If required, an alternative taxane (paclitaxel, nab-paclitaxel) [II, A] or vinorelbine [III, A] are recommended as a substitution for docetaxel.

[e]ESMO-MCBS v2.0[2] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[f]FDA approved, not EMA approved.

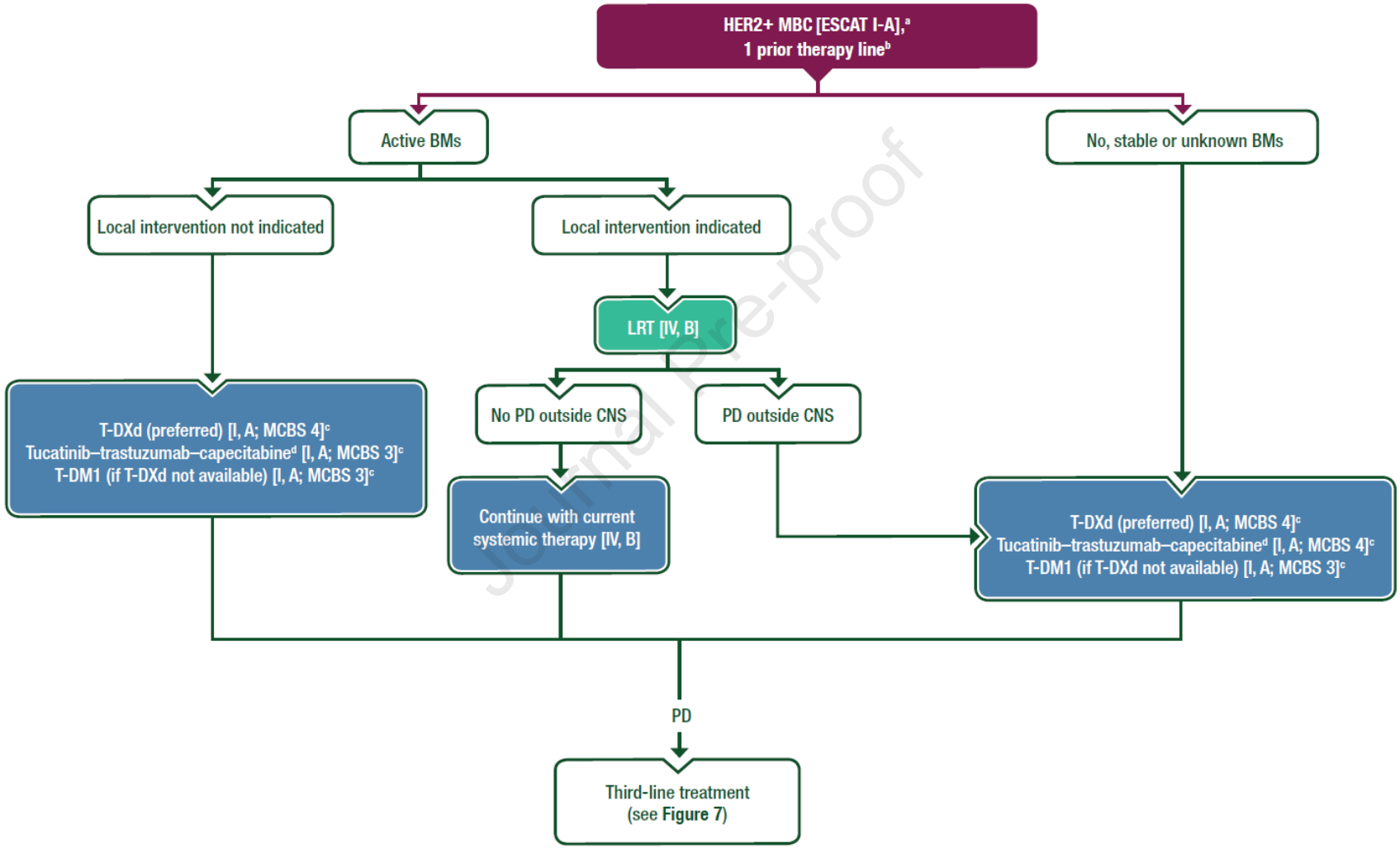
[g]EMA approved, not FDA approved.

[h]Not EMA or FDA approved.

[i]If comorbidities (e.g. cardiac disease) preclude the safe use of HER2-directed therapies.

[j]Second-line options can be recommended for patients with metastatic recurrence within 6-12 months of completing adjuvant pertuzumab–trastuzumab or T-DM1 [II, B].

Figure 6. Second-line management of HER2-positive MBC.



Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.

BM, brain metastasis; CNS, central nervous system; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; LRT, locoregional treatment; MBC, metastatic breast cancer; MCBS, Magnitude of Clinical Benefit Scale; PD, progressive disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

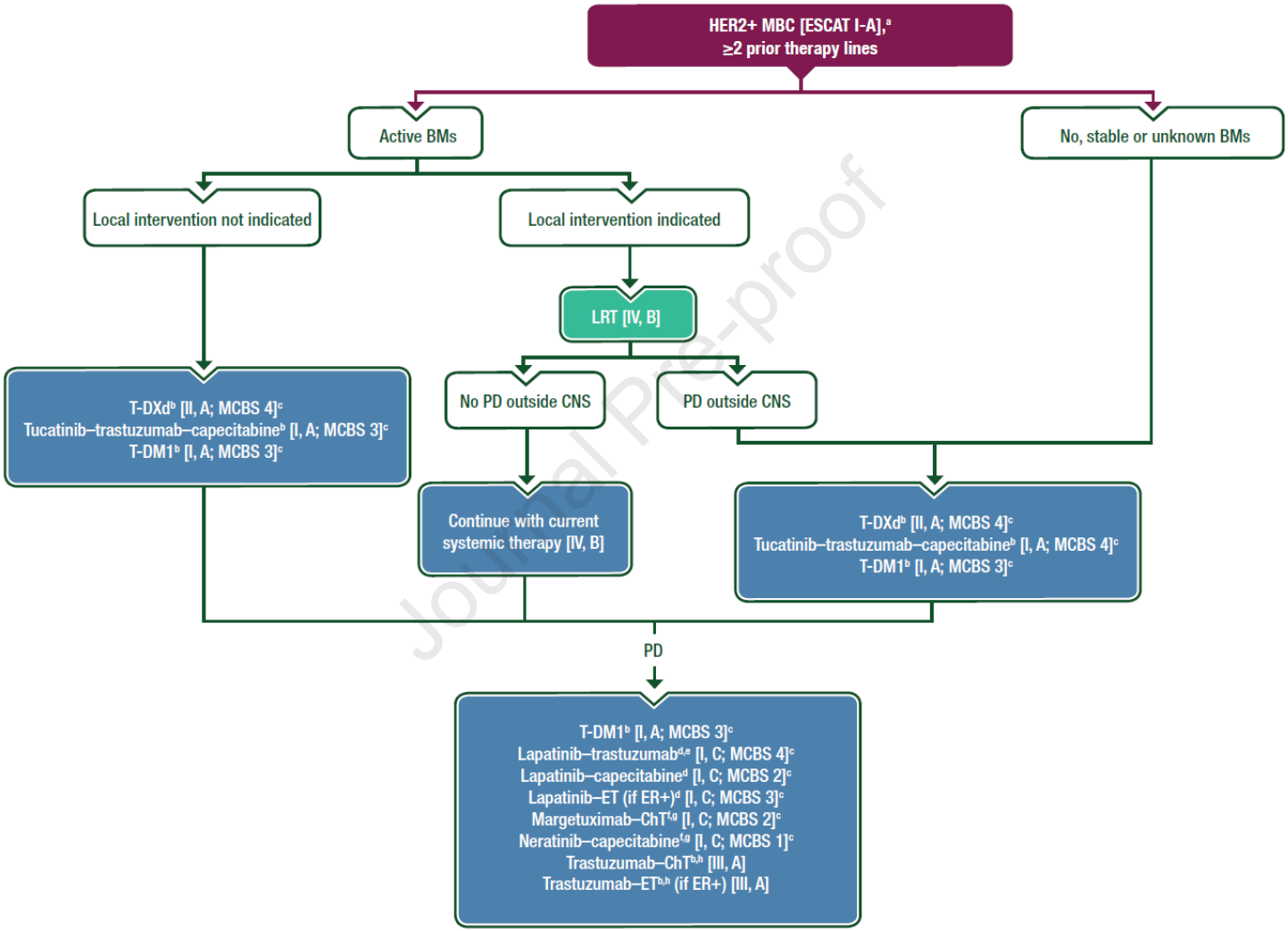
[a]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors assisted if needed by the ESMO Precision Oncology Task Force.[1]

[b]Or recurrence during or within 6-12 months of completing adjuvant treatment.

[c]ESMO-MCBS v2.0[2] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[d]FDA approved, not EMA approved in second line.

Figure 7. Third- and further-line management of HER2-positive MBC.



Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.

BM, brain metastasis; ChT, chemotherapy; CNS, central nervous system; EMA, European Medicines Agency; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; LRT, locoregional treatment; MBC, metastatic breast cancer; MCBS, Magnitude of Clinical Benefit Scale; PD, progressive disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor.

[a]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors, assisted if needed by the ESMO Precision Oncology Task Force.[1]

[b]If not used previously.

[c]ESMO-MCBS v2.0[2] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[d]No data are available on use of lapatinib after tucatinib-based therapy.

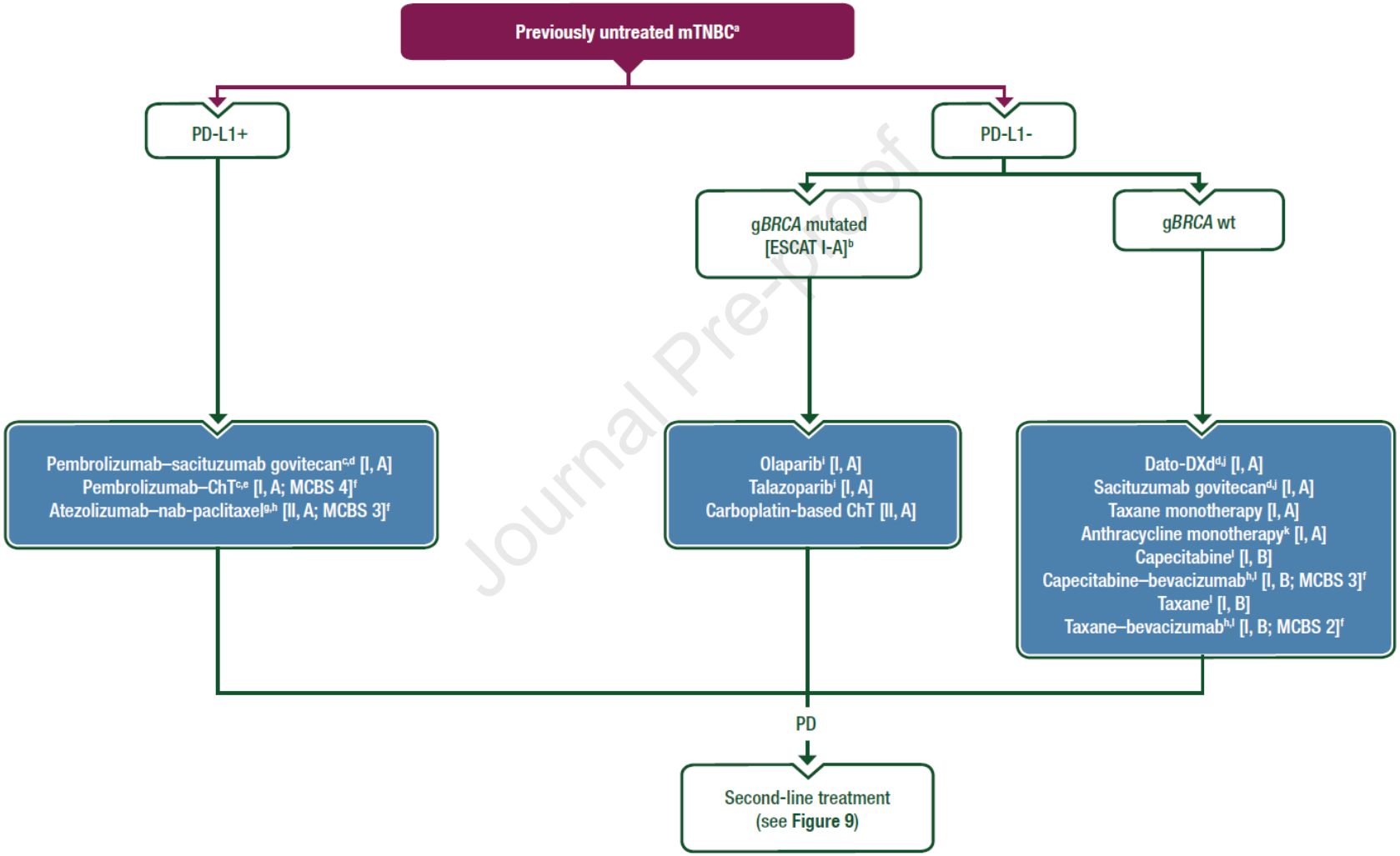
[e]EMA approved, not FDA approved.

[f]The most appropriate setting for these options may be when all standard therapy options have been exhausted [V, C], noting that there is no evidence for sequencing a TKI after a TKI in HER2-positive MBC.

[g]FDA approved, not EMA approved.

[h]When other anti-HER2 therapies have been exhausted, are not considered suitable or are not available.

Figure 8. First-line management of mTNBC.



Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.

ChT, chemotherapy; CPS, combined positive score; dato-DXd, datopotamab deruxtecan; DFI, disease-free interval; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; g, germline; ICI, immune checkpoint inhibitor; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Scale; mTNBC, metastatic triple-negative breast cancer; PD, progressive disease; PD-L1, programmed death-ligand 1; wt, wild type.

[a]*De novo* or recurrence >6 months after the end of (neo)adjuvant ICI.

[b]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors, assisted if needed by the ESMO Precision Oncology Task Force.[1]

[c]When PD-L1 CPS ≥10 and DFI ≥6 months after adjuvant treatment, noting that limited data are available after neo(adjuvant) ICI therapy.

[d]Not EMA or FDA approved.

[e]ChT is physician's choice of paclitaxel, nab-paclitaxel or carboplatin–gemcitabine.

[f]ESMO-MCBS v2.0[2] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[g]When immune cell PD-L1 positivity ≥1% and DFI ≥12 months after adjuvant treatment.

[h]EMA approved, not FDA approved.

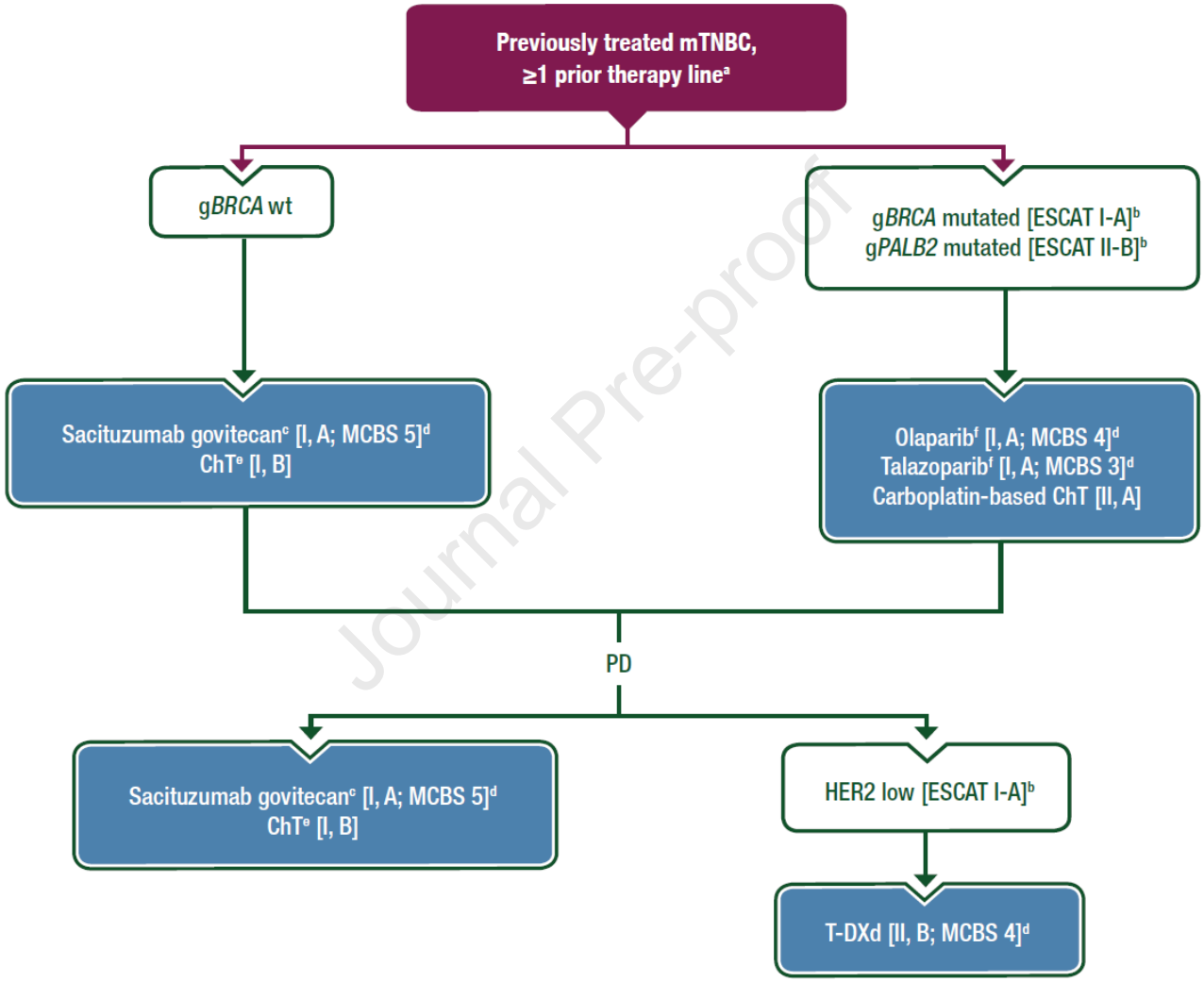
[i]Not EMA or FDA approved in first line.

[j]Recommended if available. Dato-DXd is the preferred option for patients relapsing within 6 months of adjuvant therapy [I, A].

[k]If no prior exposure or if rechallenge is possible.

[l]Preferred in case of imminent organ failure.

Figure 9. Second- and further-line management of mTNBC.



Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.

ChT, chemotherapy; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; g, germline; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Scale; mTNBC, metastatic triple-negative breast cancer; PARPi, poly (ADP-ribose) polymerase inhibitor; PD, progressive disease; T-DXd, trastuzumab deruxtecan; wt, wild type.

[a]Or recurrence ≤6-12 months after the end of (neo)adjuvant ICI.

[b]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors, assisted if needed by the ESMO Precision Oncology Task Force.[1]

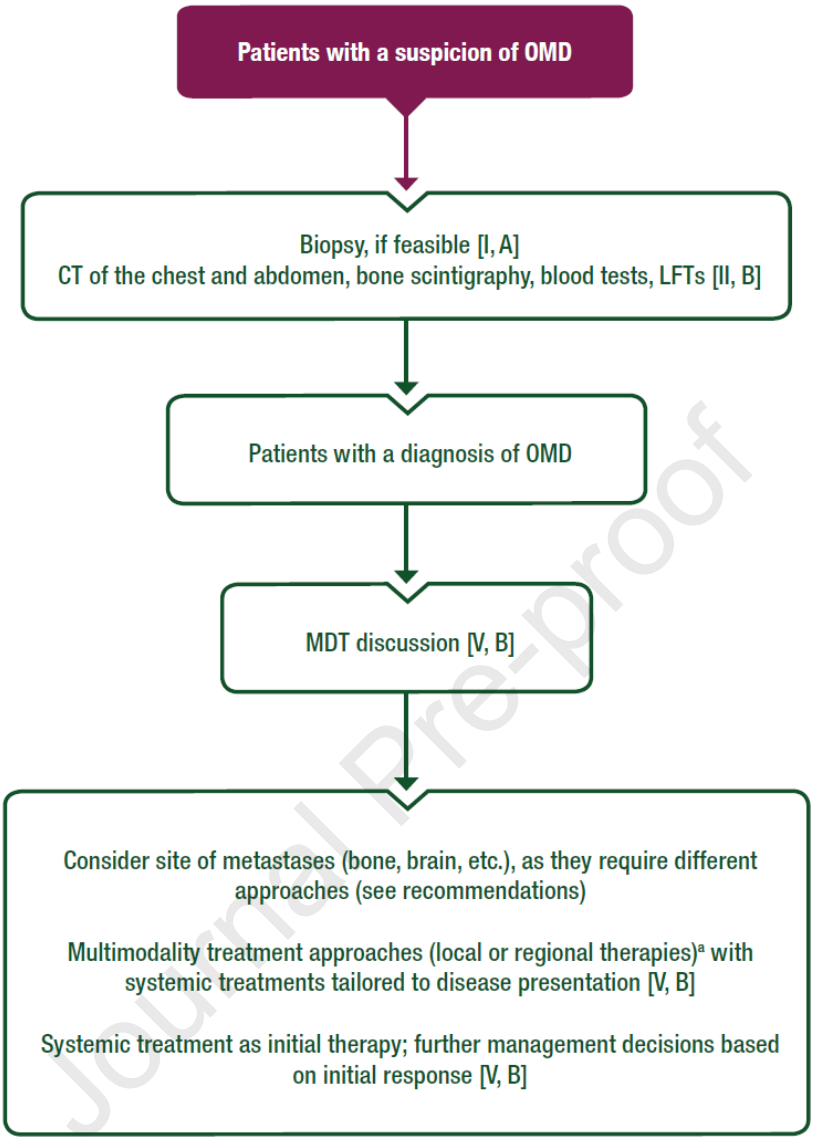
[c]If not used previously.

[d]ESMO-MCBS v2.0[2] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[e]Eribulin (ESMO-MCBS v2.0 score: 2), capecitabine or vinorelbine.

[f]If a PARPi was not used in the first-line setting.

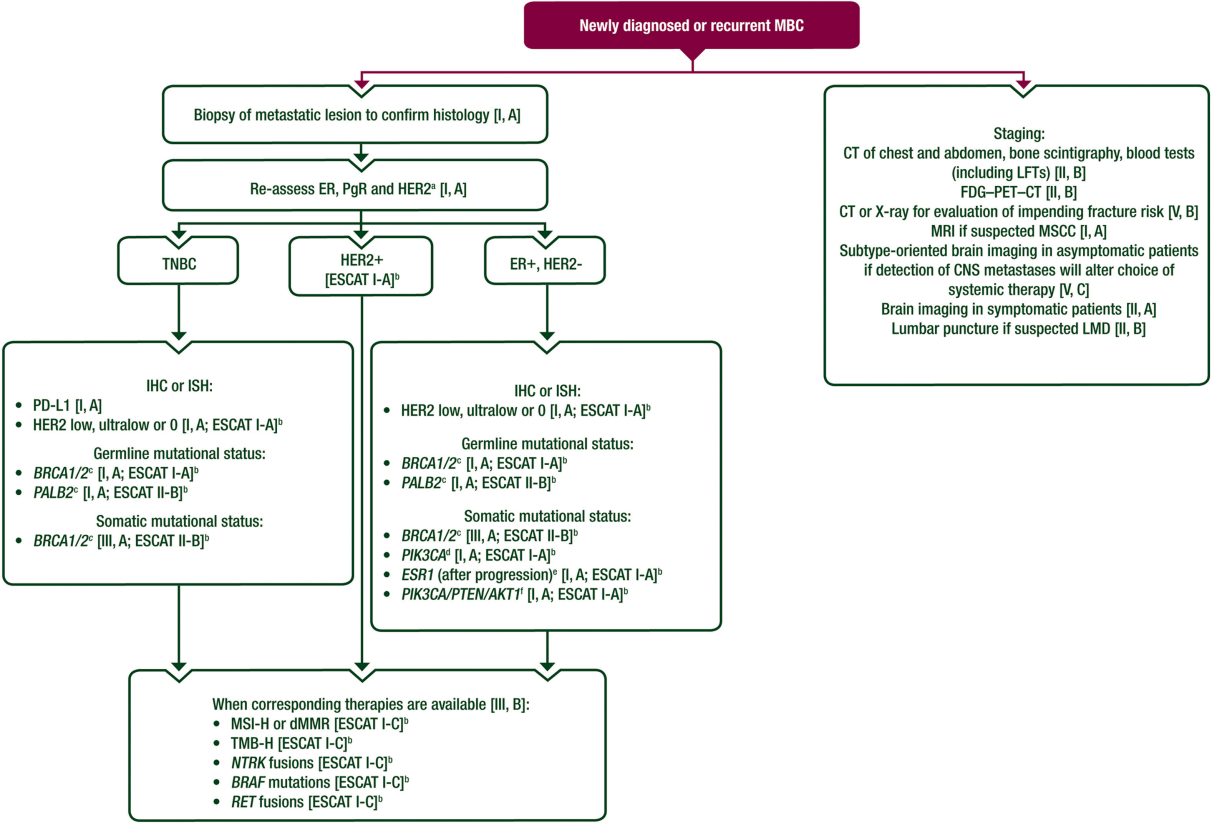
Figure 10. Site-specific management of OMD.

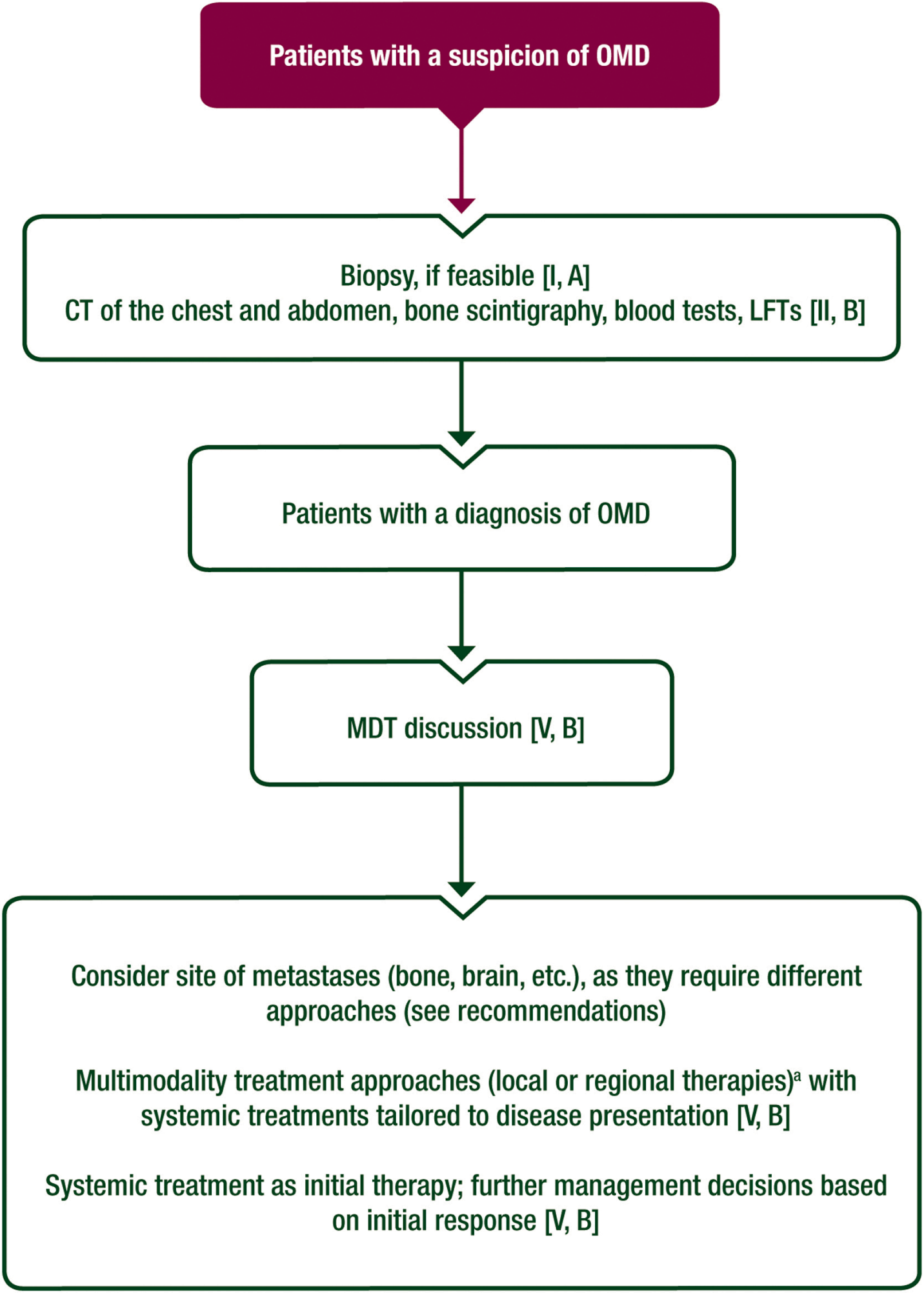


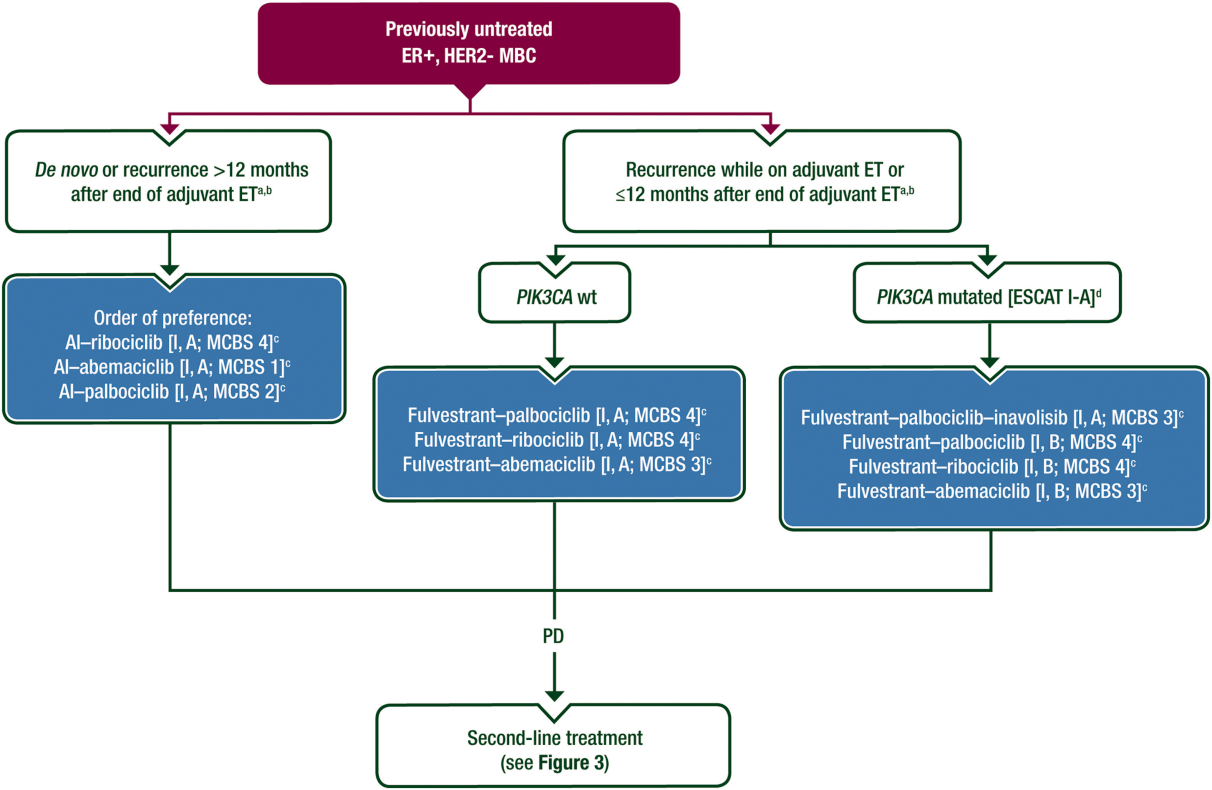
Purple: algorithm title; white: other aspects of management and non-treatment aspects.

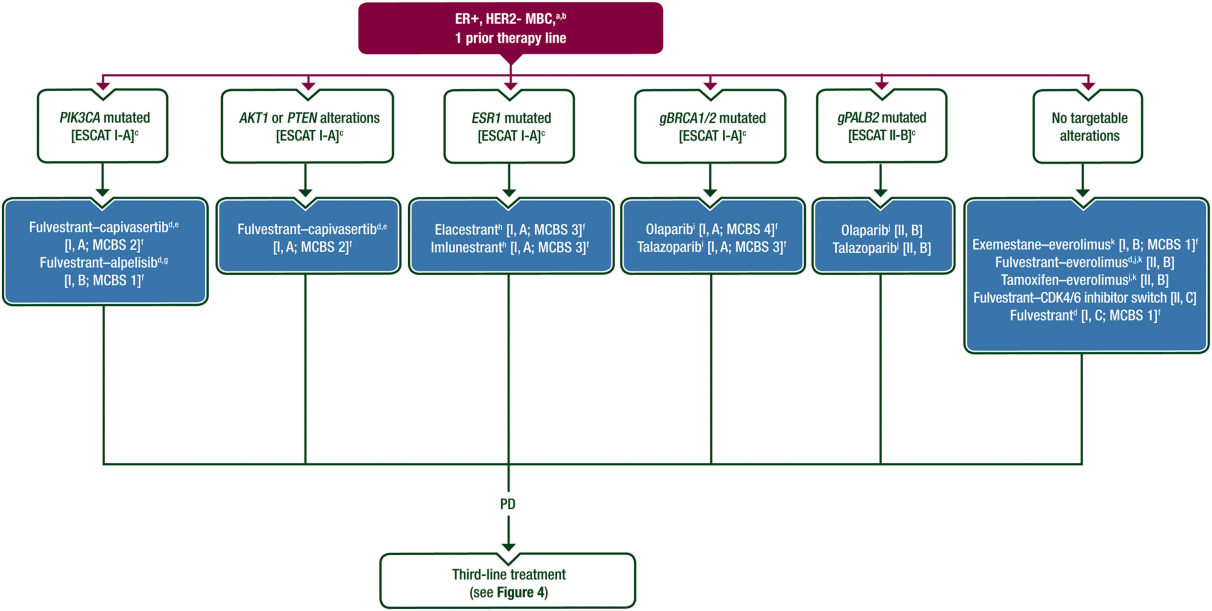
CT, computed tomography; LFT, liver function test; MDT, multidisciplinary team; OMD, oligometastatic disease.

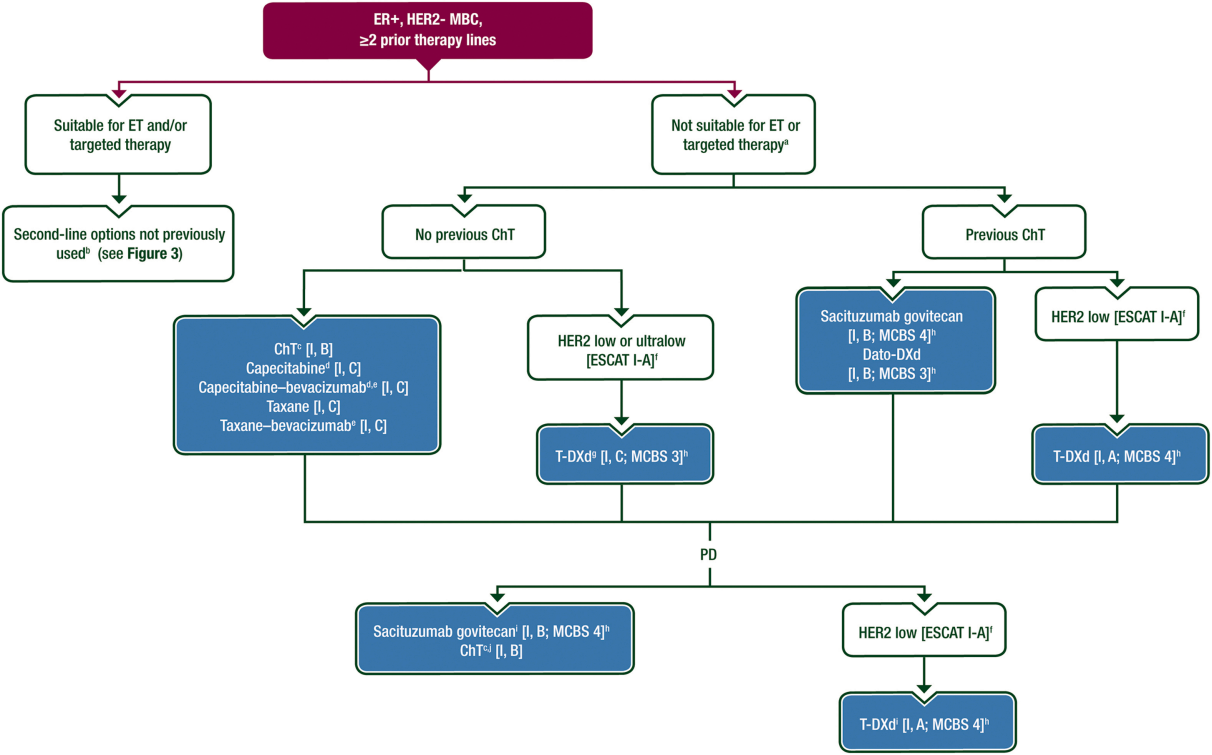
[a]Ablative procedures may be considered on a case-by-case basis for individual metastatic lesions following MDT discussion [II, C].

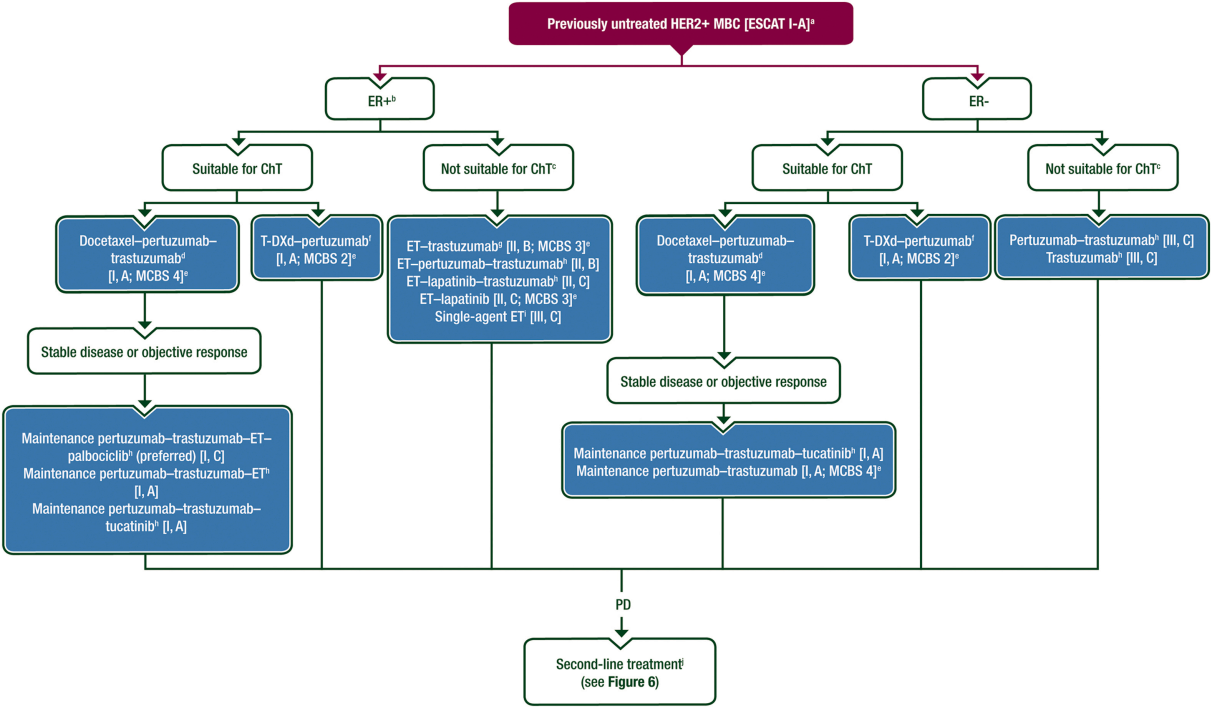

Newly diagnosed or recurrent MBC
Biopsy of metastatic lesion to confirm histology [I, A]
Re-assess ER, PgR and HER2[a] [I, A]
Staging:
CT of chest and abdomen, bone scintigraphy, blood tests (including LFTs) [II, B]
FDG–PET–CT [II, B]
CT or X-ray for evaluation of impending fracture risk [V, B]
MRI if suspected MSCC [I, A]
Subtype-oriented brain imaging in asymptomatic patients if detection of CNS metastases will alter choice of systemic therapy [V, C]
Brain imaging in symptomatic patients [II, A]
Lumbar puncture if suspected LMD [II, B]
TNBC
HER2+ [ESCAT I-A][b]
ER+, HER2-
IHC or ISH:
PD-L1 [I, A]
HER2 low, ultralow or 0 [I, A; ESCAT I-A][b]
Germline mutational status:
BRCA1/2[c] [I, A; ESCAT I-A][b]
PALB2[c] [I, A; ESCAT II-B][b]
Somatic mutational status:
BRCA1/2[c] [III, A; ESCAT II-B][b]
IHC or ISH:
HER2 low, ultralow or 0 [I, A; ESCAT I-A][b]
Germline mutational status:
BRCA1/2[c] [I, A; ESCAT I-A][b]
PALB2[c] [I, A; ESCAT II-B][b]
Somatic mutational status:
BRCA1/2[c] [III, A; ESCAT II-B][b]
PIK3CA[d] [I, A; ESCAT I-A][b]
ESR1 (after progression)[e] [I, A; ESCAT I-A][b]
PIK3CA/PTEN/AKT1[f] [I, A; ESCAT I-A][b]
When corresponding therapies are available [III, B]:
MSI-H or dMMR [ESCAT I-C][b]
TMB-H [ESCAT I-C][b]
NTRK fusions [ESCAT I-C][b]
BRAF mutations [ESCAT I-C][b]
RET fusions [ESCAT I-C][b]

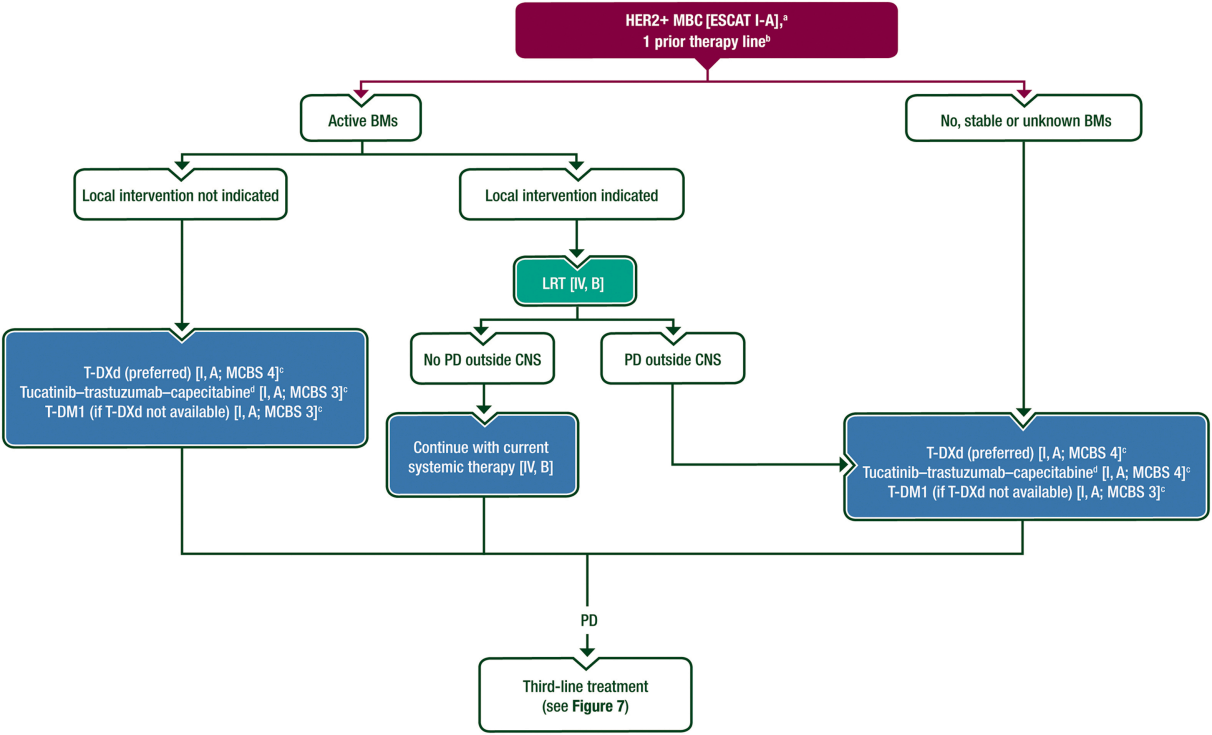

Patients with a suspicion of OMD
Biopsy, if feasible [I, A]
CT of the chest and abdomen, bone scintigraphy, blood tests, LFTs [II, B]
Patients with a diagnosis of OMD
MDT discussion [V, B]
Consider site of metastases (bone, brain, etc.), as they require different approaches (see recommendations)
Multimodality treatment approaches (local or regional therapies)[a] with systemic treatments tailored to disease presentation [V, B]
Systemic treatment as initial therapy; further management decisions based on initial response [V, B]

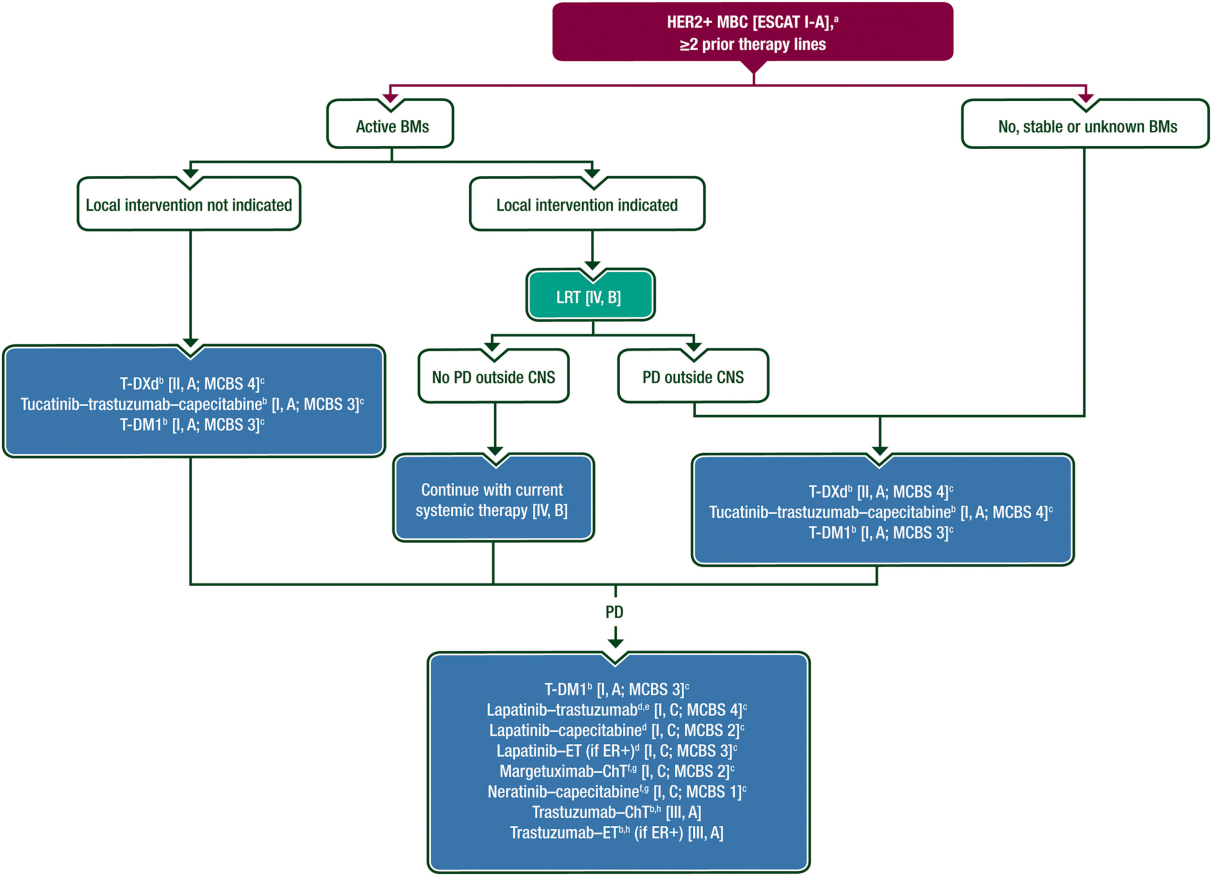

Previously untreated
ER+, HER2- MBC
De novo or recurrence >12 months after end of adjuvant ET[a,b]
Recurrence while on adjuvant ET or ≤12 months after end of adjuvant ET[a,b]
Order of preference:
AI–ribociclib [I, A; MCBS 4][c]
AI–abemaciclib [I, A; MCBS 1][c]
AI–palbociclib [I, A; MCBS 2][c]
PIK3CA wt
PIK3CA mutated [ESCAT I-A][d]
Fulvestrant–palbociclib [I, A; MCBS 4][c]
Fulvestrant–ribociclib [I, A; MCBS 4][c]
Fulvestrant–abemaciclib [I, A; MCBS 3][c]
Fulvestrant–palbociclib–inavolisib [I, A; MCBS 3][c]
Fulvestrant–palbociclib [I, B; MCBS 4][c]
Fulvestrant–ribociclib [I, B; MCBS 4][c]
Fulvestrant–abemaciclib [I, B; MCBS 3][c]
PD
Second-line treatment
(see **Figure 3**)

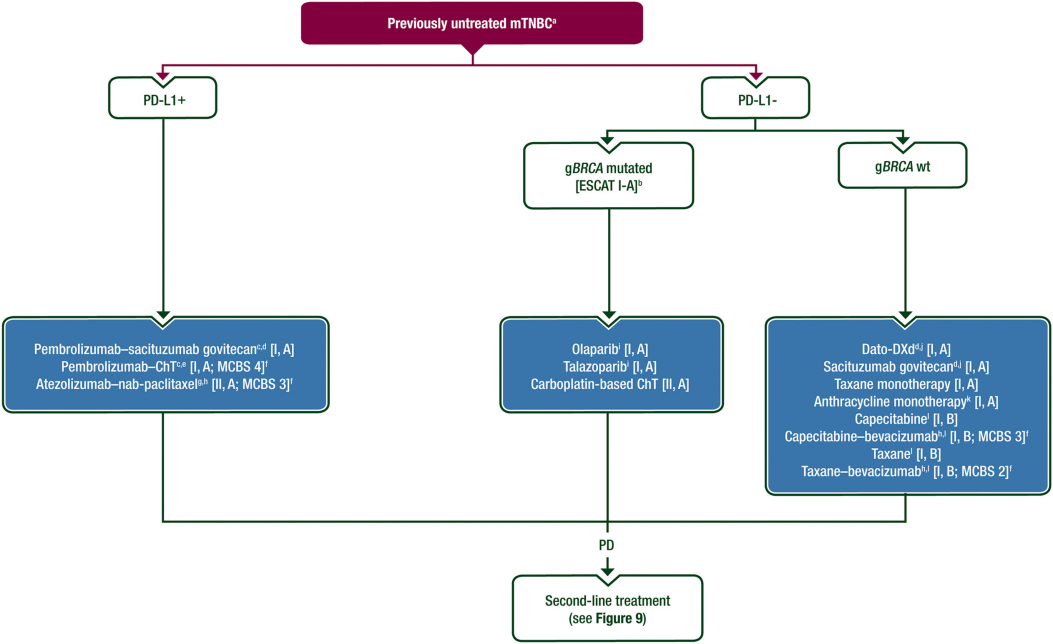

ER+, HER2- MBC,[a,b]
1 prior therapy line
PIK3CA mutated [ESCAT I-A][c]
AKT1 or PTEN alterations [ESCAT I-A][c]
ESR1 mutated [ESCAT I-A][c]
gBRCA1/2 mutated [ESCAT I-A][c]
gPALB2 mutated [ESCAT II-B][c]
No targetable alterations
Fulvestrant–capivasertib[d,e] [I, A; MCBS 2][f]
Fulvestrant–alpelisib[d,g] [I, B; MCBS 1][f]
Fulvestrant–capivasertib[d,e] [I, A; MCBS 2][f]
Elacestrant[h] [I, A; MCBS 3][f]
Imlunestrant[h] [I, A; MCBS 3][f]
Olaparib[i] [I, A; MCBS 4][f]
Talazoparib[i] [I, A; MCBS 3][f]
Olaparib[j] [II, B]
Talazoparib[j] [II, B]
Exemestane–everolimus[k] [I, B; MCBS 1][f]
Fulvestrant–everolimus[d,j,k] [II, B]
Tamoxifen–everolimus[j,k] [II, B]
Fulvestrant–CDK4/6 inhibitor switch [II, C]
Fulvestrant[d] [I, C; MCBS 1][f]
PD
Third-line treatment
(see Figure 4)

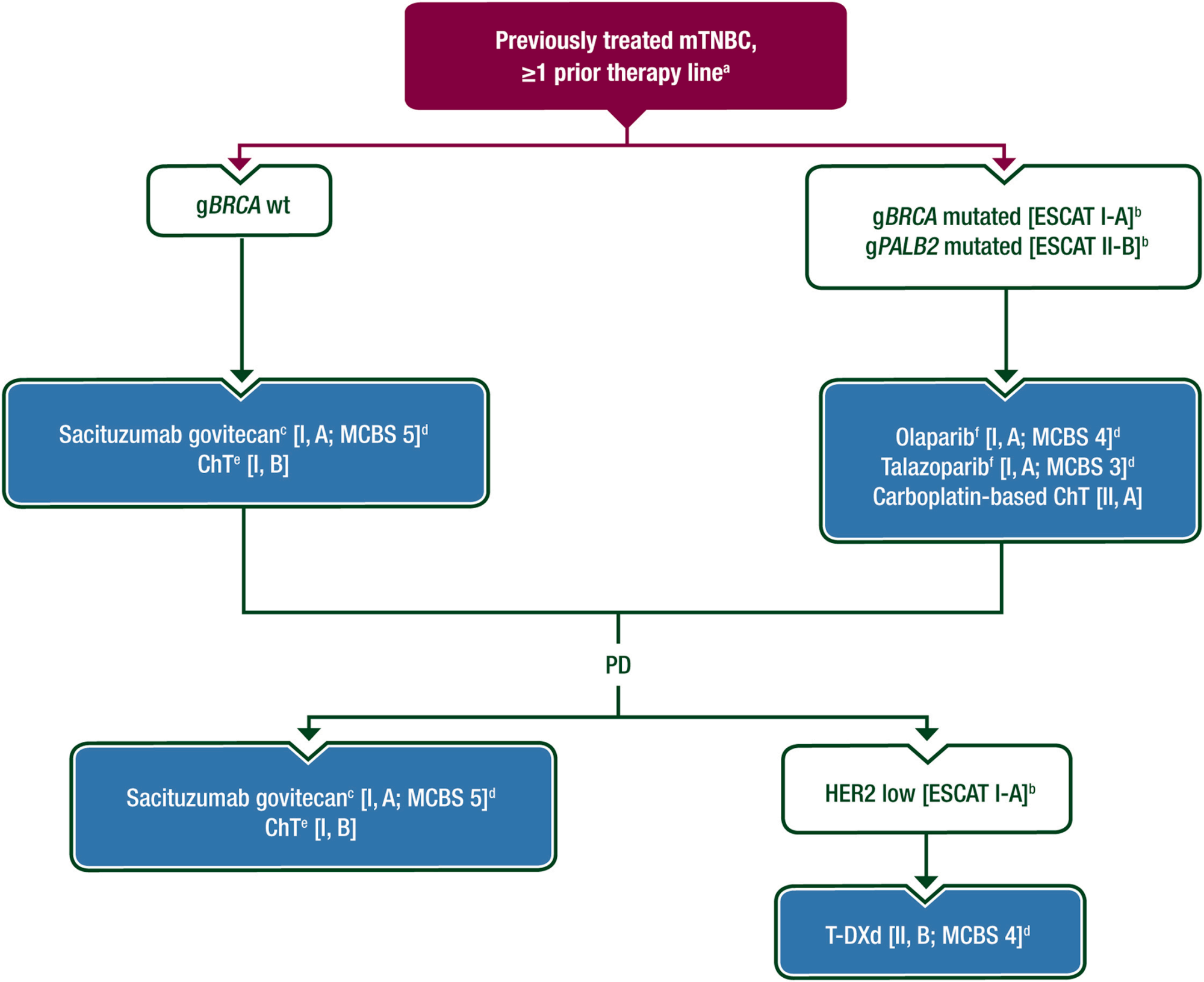

ER+, HER2- MBC,
≥2 prior therapy lines
Suitable for ET and/or targeted therapy
Second-line options not previously used[b] (see Figure 3)
Not suitable for ET or targeted therapy[a]
No previous ChT
Previous ChT
ChT[c] [I, B]
Capecitabine[d] [I, C]
Capecitabine–bevacizumab[d,e] [I, C]
Taxane [I, C]
Taxane–bevacizumab[e] [I, C]
HER2 low or ultralow [ESCAT I-A][f]
T-DXd[g] [I, C; MCBS 3][h]
Sacituzumab govitecan [I, B; MCBS 4][h]
Dato-DXd [I, B; MCBS 3][h]
HER2 low [ESCAT I-A][f]
T-DXd [I, A; MCBS 4][h]
PD
Sacituzumab govitecan[i] [I, B; MCBS 4][h]
ChT[c,i] [I, B]
HER2 low [ESCAT I-A][f]
T-DXd[i] [I, A; MCBS 4][h]


Previously untreated HER2+ MBC [ESCAT I-A][a]
ER+[b]
ER-
Suitable for ChT
Not suitable for ChT[c]
Suitable for ChT
Not suitable for ChT[c]
Docetaxel–pertuzumab–trastuzumab[d] [I, A; MCBS 4][e]
T-DXd–pertuzumab[f] [I, A; MCBS 2][e]
ET–trastuzumab[g] [II, B; MCBS 3][e]
ET–pertuzumab–trastuzumab[h] [II, B]
ET–lapatinib–trastuzumab[h] [II, C]
ET–lapatinib [II, C; MCBS 3][e]
Single-agent ET[i] [III, C]
Docetaxel–pertuzumab–trastuzumab[d] [I, A; MCBS 4][e]
T-DXd–pertuzumab[f] [I, A; MCBS 2][e]
Pertuzumab–trastuzumab[h] [III, C]
Trastuzumab[h] [III, C]
Stable disease or objective response
Stable disease or objective response
Maintenance pertuzumab–trastuzumab–ET–palbociclib[h] (preferred) [I, C]
Maintenance pertuzumab–trastuzumab–ET[h] [I, A]
Maintenance pertuzumab–trastuzumab–tucatinib[h] [I, A]
Maintenance pertuzumab–trastuzumab–tucatinib[h] [I, A]
Maintenance pertuzumab–trastuzumab [I, A; MCBS 4][e]
PD
Second-line treatment[j] (see Figure 6)


HER2+ MBC [ESCAT I-A],[a]
1 prior therapy line[b]
Active BMs
No, stable or unknown BMs
Local intervention not indicated
Local intervention indicated
LRT [IV, B]
No PD outside CNS
PD outside CNS
T-DXd (preferred) [I, A; MCBS 4][c]
Tucatinib–trastuzumab–capecitabine[d] [I, A; MCBS 3][c]
T-DM1 (if T-DXd not available) [I, A; MCBS 3][c]
Continue with current systemic therapy [IV, B]
T-DXd (preferred) [I, A; MCBS 4][c]
Tucatinib–trastuzumab–capecitabine[d] [I, A; MCBS 4][c]
T-DM1 (if T-DXd not available) [I, A; MCBS 3][c]
PD
Third-line treatment
(see Figure 7)


HER2+ MBC [ESCAT I-A],[a]
≥2 prior therapy lines
Active BMs
No, stable or unknown BMs
Local intervention not indicated
Local intervention indicated
LRT [IV, B]
T-DXd[b] [II, A; MCBS 4][c]
Tucatinib–trastuzumab–capecitabine[b] [I, A; MCBS 3][c]
T-DM1[b] [I, A; MCBS 3][c]
No PD outside CNS
PD outside CNS
Continue with current systemic therapy [IV, B]
T-DXd[b] [II, A; MCBS 4][c]
Tucatinib–trastuzumab–capecitabine[b] [I, A; MCBS 4][c]
T-DM1[b] [I, A; MCBS 3][c]
PD
T-DM1[b] [I, A; MCBS 3][c]
Lapatinib–trastuzumab[d,e] [I, C; MCBS 4][c]
Lapatinib–capecitabine[d] [I, C; MCBS 2][c]
Lapatinib–ET (if ER+)[d] [I, C; MCBS 3][c]
Margetuximab–ChT[f,g] [I, C; MCBS 2][c]
Neratinib–capecitabine[f,g] [I, C; MCBS 1][c]
Trastuzumab–ChT[b,h] [III, A]
Trastuzumab–ET[b,h] (if ER+) [III, A]


Previously untreated mTNBC[a]
PD-L1+
PD-L1-
gBRCA mutated [ESCAT I-A][b]
gBRCA wt
Pembrolizumab–sacituzumab govitecan[c,d] [I, A]
Pembrolizumab–ChT[c,e] [I, A; MCBS 4][f]
Atezolizumab–nab-paclitaxel[g,h] [II, A; MCBS 3][f]
Olaparib[i] [I, A]
Talazoparib[i] [I, A]
Carboplatin-based ChT [II, A]
Dato-DXd[d,j] [I, A]
Sacituzumab govitecan[d,j] [I, A]
Taxane monotherapy [I, A]
Anthracycline monotherapy[k] [I, A]
Capecitabine[l] [I, B]
Capecitabine–bevacizumab[h,j] [I, B; MCBS 3][f]
Taxane[l] [I, B]
Taxane–bevacizumab[h,j] [I, B; MCBS 2][f]
PD
Second-line treatment (see Figure 9)


Previously treated mTNBC,
≥1 prior therapy line[a]
gBRCA wt
gBRCA mutated [ESCAT I-A][b]
gPALB2 mutated [ESCAT II-B][b]
Sacituzumab govitecan[c] [I, A; MCBS 5][d]
ChT[e] [I, B]
Olaparib[f] [I, A; MCBS 4][d]
Talazoparib[f] [I, A; MCBS 3][d]
Carboplatin-based ChT [II, A]
PD
Sacituzumab govitecan[c] [I, A; MCBS 5][d]
ChT[e] [I, B]
HER2 low [ESCAT I-A][b]
T-DXd [II, B; MCBS 4][d]