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Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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incidence and epidemiology

Breast cancer is the most common cancer in women in almost all countries, including developing countries. In 2008, 1 380 000 new cases and 458 000 breast cancer deaths were noted in the world and 332 000 new cases/89 000 deaths in the European Union. The age-standardized incidence in Europe was 62.8/100 000 and the mortality—16.7/100 000 women/year. Since 1990, the incidence rate has increased 1.5% annually. Owing to advances both in early detection and in adjuvant systemic therapy, mortality rates from breast cancer have been decreasing steadily in most Western countries since the early 1990s. However, it is still the leading cause of cancer death in women in both developing (269 000 deaths, 12.7% of total) and developed (189 000 deaths, 15.5% of total) regions. Approximately 5% to 10% of breast cancers are metastatic at diagnosis; of these, approximately one-fifth will survive 5 years. Depending on prognostic factors, up to 30% of node-negative and up to 70% of node-positive breast cancers will relapse. The prevalence of metastatic disease is high because many women live with this disease for several years; there is however, a major lack of accurate data on this prevalence in the great majority of countries since most cancer registries do not capture relapses. As there are significant variations in outcomes of early breast cancer among different regions, the burden of metastatic breast cancer (MBC) may differ from that of early disease.

diagnosis and pathology

Clinical suspicion must be confirmed by imaging. A minimal staging work-up should include a complete history and physical examination, hematology and biochemistry tests, imaging of chest, abdomen and bone; in certain situations, information may be provided by functional imaging such as PET–CT (positron emission tomography–computed tomography scan), DCE-MRI (dynamic contrast-enhanced magnetic resonance imaging) or MR-DWI (diffusion-weighted magnetic resonance) (in particular, in case of equivocal results of routine imaging or when these exams fail to detect the location of the relapse, or when pathology from suspicious lesion cannot be obtained).

Efforts should be made to obtain histopathological confirmation whenever technically feasible, particularly in the situation of an isolated metastatic lesion. Biological markers important for treatment decisions, such as steroid hormone receptors (ER, PR) and HER-2 status should be re-evaluated, at least once, in a metastatic lesion. Although there are no data to support the choice of therapy in case of discordance in HR/HER-2 status between primary and metastatic tumor, retrospective data suggest inferior outcome in 'discordant' patients (possibly due to inappropriate treatment, not adjusted for biomarker changes). It seems appropriate to recommend that, if at any given biopsy the receptors were positive, targeted therapy (endocrine and/or anti-HER-2 therapy) should be provided.

There is no proven value of routine 'screening' tests for metastatic disease in asymptomatic early breast cancer patients. However, the available data are from a time when neither biological therapy nor effective (in terms of local control) and less invasive (in terms of quality of life and side-effects) locoregional therapeutic techniques, such as radiosurgery for central nervous system (CNS) metastases or radiofrequency ablation for liver metastases, were available. In addition, new detection techniques are now available, such as MRI, PET-scan, PET–CT and others, that may allow the detection of very early metastatic disease. Therefore, new studies are needed to evaluate the role of early diagnosis of metastatic disease in the current context.

The occurrence of locoregional recurrence is often associated with distant spread and such patients should undergo full staging procedures before undergoing local treatments.

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Table 1. Staging and assessment of prognosis

Complete history, including
menopausal status
co-morbidities (e.g. cardiac diseases, diabetes mellitus, thromboembolic diseases, renal or liver disease)
detailed history of the primary tumor, its biology, management and status at the last follow-up
history of recurrent/metastatic disease, including duration, previous sites of involvement, previous treatments and their effect
current symptoms, performance status, socio-economic background and preferences (Table 2)
Detailed physical examination
Blood and other laboratory tests: complete blood count, liver and renal function tests, alkaline phosphatase, LDH, calcium and, if applicable, specific tests required for particular treatments such as urinary protein. The clinical value of tumor markers for diagnostic purposes has not been proven. However, they may assist in evaluating response to treatment (i.e. monitoring), particularly in patients with non-measurable disease
Assessment of visceral disease
Chest: preferably CT; chest X-ray has low sensitivity and should be replaced by chest CT whenever possible
Abdomen: ultrasound, CT (preferably) or MRI
Bone scan, with confirmation of lesions and further work-up (i.e. fracture risk, etc.) if needed by X-ray/CT/MRI
CT and/or MRI of the CNS should be symptom-driven; the value of 'screening' for asymptomatic brain metastases, even in breast cancer subtypes with higher risk of developing CNS involvement (HER-2-positive and triple-negative breast cancer), is not established and should not be carried out routinely
All imaging should be carried out in a way that will allow for future comparative assessment to evaluate the treatment effect
PET/PET–CT should not be used routinely as part of the initial work-up but can be useful for identifying the site of relapse when traditional imaging methods are equivocal or conflicting. It may also be helpful to identify or confirm isolated locoregional relapse or isolated metastatic lesions, a situation where patients may benefit from a more aggressive multidisciplinary approach
Estrogen, progesterone and HER-2 receptors of the metastatic lesion should be obtained at least once in the evolution of the disease, if technically possible, and particularly if not available from the primary tumor
Cardiac assessments, in particular in HER-2-positive patients and those considered for anthracycline-based chemotherapy
Circulating tumor cells are still an experimental technique and should not be used outside a clinical trial
In case of lesions inaccessible for biopsy, functional imaging such as PET–CT, DCE-MRI or MR-DWI may be helpful to confirm their malignant character

The value of multigene assays used for recurrence risk assessment in early breast cancer has not been confirmed in advanced disease.

treatment: general statements

locoregional recurrence

Whenever possible, isolated locoregional recurrence should be treated with a curative intent (Figure 1). If feasible, complete excision of recurrent tumor is recommended. In patients previously treated by breast-conserving surgery, a mastectomy should be carried out [III, A]. In patients not previously irradiated, full-dose radiotherapy to chest wall and regional lymph node areas should be given [III, A]. In those previously irradiated, re-irradiation to limited areas of the chest wall may be applied, taking into consideration the duration of radiation-free period, intensity of existing late radiation effects and the risk of additional local–regional relapse [III, B]. Inoperable patients can, if feasible, undergo radical radiotherapy to chest wall and regional lymph node areas with boost to macroscopic disease sites. However, in these patients, primary systemic therapy to decrease the size of the tumor and render it operable is preferred [III, B].

Table 2. Factors to consider in risk assessment and treatment decision-making for MBC

Disease-related factors	Patient-related factors
Disease-free interval	Patient preferences
Previous therapies and response	Biological age
Biological factors (hormonal receptors, HER-2)	Menopausal status
Tumor burden (number and site of metastases)	Co-morbidities and performance status
Need for rapid disease/symptom control	Socio-economic and psychological factors
	Therapies available in the patient's country

The value of 'secondary' or 'pseudo-adjuvant' systemic treatment is not well proven. The role of chemotherapy in this setting is a subject of ongoing randomized studies [II, B]. Factors such as tumor biology and aggressiveness, prior adjuvant systemic therapy, patient co-morbidities and preferences should all be taken into account when deciding whether to propose 'pseudo-adjuvant' chemotherapy (expert opinion). Although not well proven, 'pseudo-adjuvant' endocrine therapy is a reasonable option in view of its expected benefit and low toxicity [II, B]. 'Pseudo-adjuvant' trastuzumab therapy is also acceptable, particularly in cases where adjuvant trastuzumab was not prescribed at the time of initial diagnosis (expert opinion).

In patients not suitable for local treatment with curative intent (e.g. inoperable, previously irradiated), systemic therapies remain the mainstay of treatment. Their choice depends on tumor biology, previous systemic treatments, duration of disease-free interval, patient co-morbidities and preferences.

metastatic disease

The management of MBC should involve all appropriate specialties in a multi/interdisciplinary team (medical, radiation, surgical and imaging oncologists, palliative care specialist, psychosocial support), and patients should be offered personalized appropriate psychosocial, supportive and symptom-related interventions as a routine part of their care.

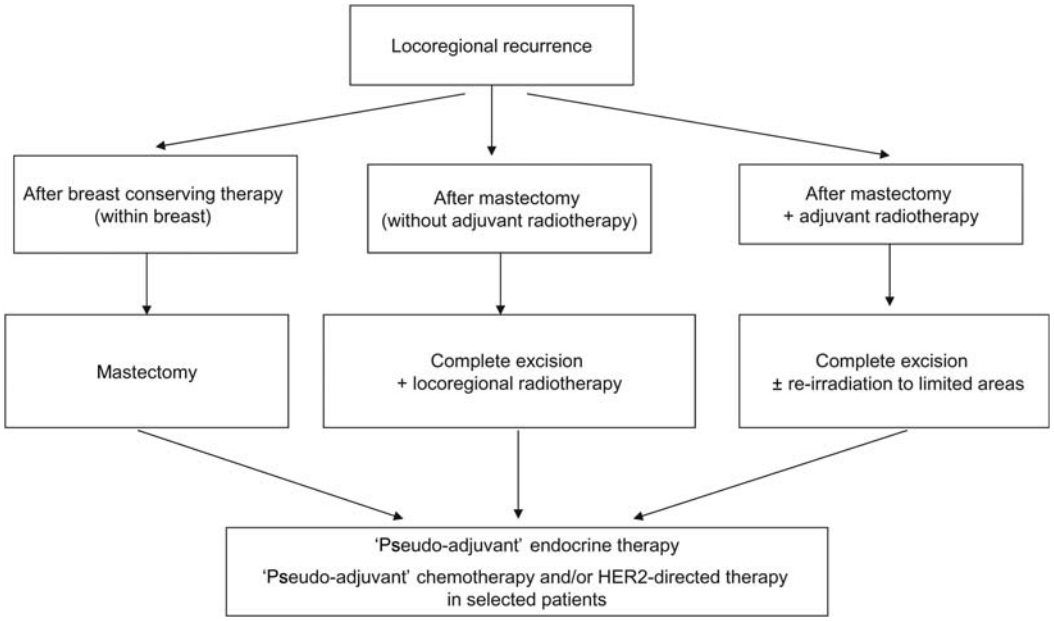


Figure 1 Management of locoregional recurrence.

Specialist breast nurses can provide crucial support, as well as coordination and continuity of care for patients with advanced breast cancer and should be available to all patients. Countries in which this nurse subspecialty does not yet exist, should make all efforts to establish it.

There are only a few proven standards of care in MBC management, therefore well-designed, independent, prospective randomized trials are a priority. Participation in such clinical trials should be offered to all eligible patients, whenever available.

The vast majority of MBC is incurable and hence the main treatment goal is palliation, with the aim of maintaining/improving quality of life and possibly prolonging survival.

The realistic treatment goals should be discussed with the patient and her/his caregivers from the beginning and the patient should be encouraged to actively participate in all decisions. Patient preferences should always be taken into account.

Systemic treatment options for MBC are endocrine therapy, chemotherapy, bone-directed agents (e.g. bisphosphonates, denosumab) and targeted biological agents such as trastuzumab and lapatinib [I, A].

The choice of therapy should be made after consideration of factors listed in Table 2.

For the majority of patients, overall survival outcomes from sequential use of single-cytotoxic drugs are equivalent to combination chemotherapy. The choice between these options should primarily take into account the need for a rapid and significant response, as well as quality of life. In patients without directly life-threatening or severely symptomatic disease, single-agent chemotherapy is the preferred option.

Duration of each regimen and number of regimens should be tailored to each individual patient.

In HR-positive and HER-2-negative disease, endocrine therapy is the treatment of first choice independent of metastatic site, unless rapid response is needed. Limited visceral metastases are not a contraindication for endocrine therapy. Chemo and endocrine therapy should not be given concomitantly. Given its low toxicity, endocrine maintenance should be considered.

In patients with HER2, overexpressing/amplified early incorporation of targeted anti-HER-2 agents is highly recommended unless specific contra-indications exist.

The most common indications for palliative radiotherapy include:

Bone metastases which are painful or carry a risk of fracture and/or neurological complications (radiotherapy options include 'limited field' external beam irradiation, hemi-body irradiation and application of radioactive 'bone-seeking' isotopes);
Brain metastases—patients with extensive cerebral involvement usually require whole-brain radiotherapy (WBRT); in those with single or few metastatic foci, stereotactic radiosurgery can be used as an alternative to surgical resection, with improvement in local control and less side-effects than WBRT; addition of WBRT to surgery or stereotactic radiosurgery decreases the number of intracranial relapses but increases substantially side-effects, mainly cognitive, and should be discussed with the patient;
Painful or fungating soft-tissue masses.

For limited metastatic presentations, surgery or radical radiotherapy may be considered. Systemic tumor control should be the prerequisite for tumor-reduction local therapy in metastatic disease. Although no randomized data exist, a bulk of retrospective data suggest a significant survival benefit from the removal of the primary tumor (with clear margins) in patients

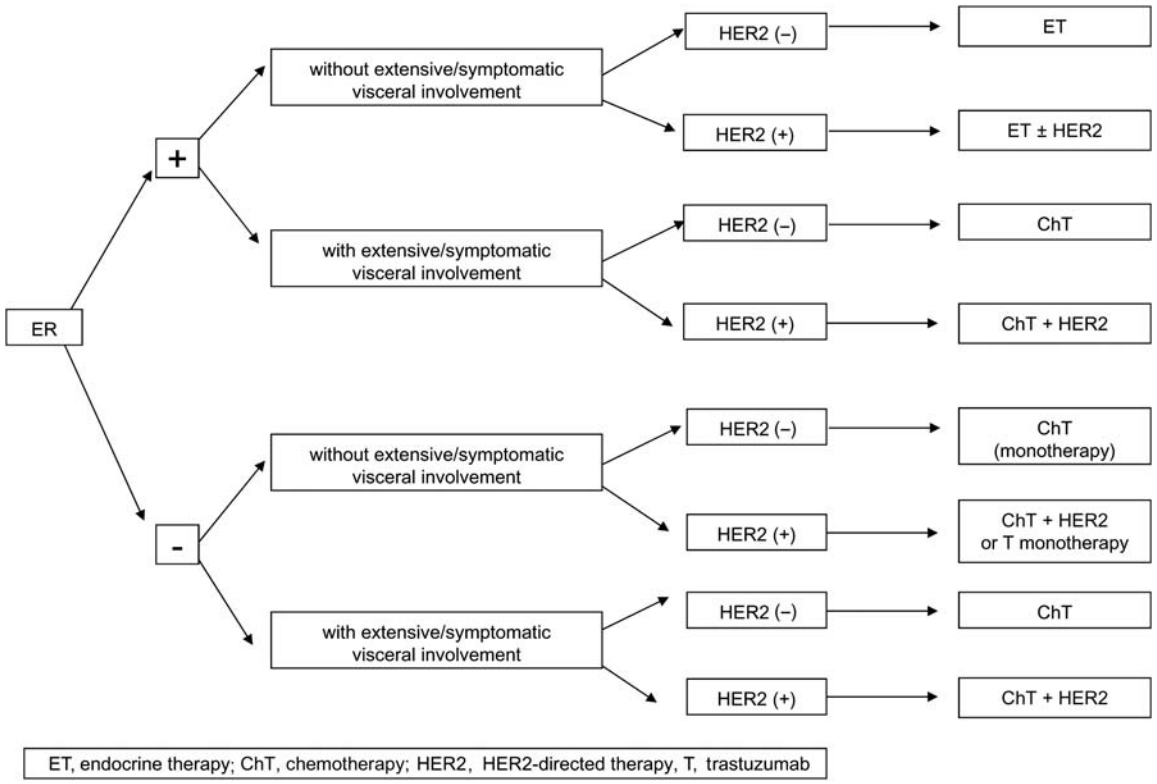


Figure 2 First-line systemic therapy for advanced breast cancer.

with primary metastatic disease. Prospective randomized trials addressing this question are currently ongoing.

Palliative surgery may be utilized to prevent or stabilize pathological fractures, remove fungating soft-tissue masses or relieve compression leading to neurological deficits.

Bisphosphonates or RANK-ligand antibody denosumab should be used for the treatment of clinically evident bone metastases (to palliate symptoms and decrease risk of bone events) [I, A]. Bone-directed therapy should be started following a diagnosis of bone metastases. Although the optimal duration of these treatments is unknown and the benefit of duration beyond 2 years has not been demonstrated in clinical trials, an ongoing risk of skeletal events persists, especially at times of disease progression and thus long-term treatment seems appropriate. The impact of bisphosphonate or denosumab-associated side-effects (including osteonecrosis of the jaw and nephrotoxicity) is minor, and for the vast majority of patients the benefit of treatment outweighs the risks. The choice between bisphosphonates and denosumab depends on drug availability, presence of possible contraindications (renal insufficiency) and patient preferences.

A multi-disciplinary discussion including pain control experts, radiation oncologists, medical oncologists, surgeons specialized in bone treatment and radiologists with expertise in vertebroplasty/kyphoplasty is crucial to determine the best therapeutic approach for the individual patient. A pathway for rapid (within 24 h) assessment of patients with spinal cord compression should be available with access to specialist spinal surgeons for decompression and stabilization of compressing or unstable spinal lesions when clinically appropriate.

Malignancy-related hypercalcemia should be treated with bisphosphonates and intravenous fluids.

The choice of drugs for MBC, their timing, optimal duration, methods of administration and side-effects should be considered individually, taking into account patient preferences, expected treatment acceptance and adherence. Availability and reimbursement issues must also be taken into account.

treatment-specific breast cancer subtypes

luminal breast cancer (hormone receptor-positive, irrespective of HER-2 status) (Figure 2)

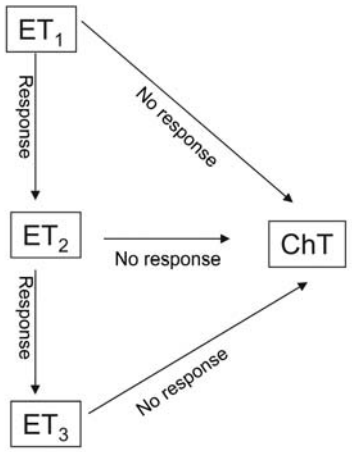
Endocrine therapy is the preferred option except if clinically aggressive disease mandates a quicker response or if there are doubts regarding endocrine responsiveness of the tumor. Available endocrine agents are listed in Table 3.

The choice of endocrine agent should be based on menopausal status, co-morbidities, agents received in the adjuvant setting and the drug safety profile.

Apart from combination of ovarian suppression with tamoxifen [or aromatase inhibitors (AIs)] in premenopausal patients, there is no rationale for the use of combination endocrine therapies.

Table 3. Available endocrine therapies for MBC

Class of agent	
Selective estrogen receptor modulators	Tamoxifen; toremifene
Estrogen receptor down-regulator	Fulvestrant
Luteinizing hormone-releasing hormone analogues	Goserelin, leuprorelin, triptorelin
Third-generation aromatase inhibitors	
Non-steroidal	Anastrozole, letrozole
Steroidal	Exemestane
Progestins	Medroxyprogesterone acetate; megestrol acetate
Anabolic steroids	Nandrolone decanoat
Estrogens	Estrogens



ET, endocrine therapy; ChT, chemotherapy

Figure 3 Management of endocrine-responsive advanced breast cancer.

The value of maintenance endocrine treatment after chemotherapy has not been confirmed by controlled clinical studies, but—given its low toxicity and potential benefits—is a reasonable approach (expert opinion).

Concomitant chemo-endocrine therapy should not be used outside clinical trials.

In case of ER-positive/HER-2-positive breast cancer with no indication for chemotherapy, endocrine therapies should be combined with anti-HER-2 therapies (trastuzumab, lapatinib) since they lead to a significant improvement in progression free survival (in this case equivalent to 'time without chemotherapy'), although no benefit in overall survival, compared with endocrine therapy alone.

premenopausal patients

If no prior adjuvant tamoxifen or if discontinued for >12 months, tamoxifen with ovarian ablation (luteinizing hormone-releasing hormone analogue, surgery or ovarian irradiation) is the preferred option [I, B]. Further treatment lines (in patients with ovarian ablation/suppression) do not differ from those used in postmenopausal population (as described below).

postmenopausal patients

If not used in the adjuvant setting or if discontinued for >12 months, AIs (anastrozole, letrozole, exemestane) are the preferred option since they have consistently shown superior results to tamoxifen as first-line therapy in terms of response rate, time to progression and, for letrozole, in 2-year overall survival [II, A]. Preferably, a nonsteroidal AI should be used after progression on a steroidal AI and vice versa. The risk of accelerated bone loss needs to be considered and calcium and vitamin D supplements are recommended.

Tamoxifen remains an acceptable first-line therapy. Although definitive data are still needed, it seems reasonable to advise patients under tamoxifen to avoid, whenever possible, the use of drugs modulating the activity of CYP2D6, such as some selective serotonin reuptake inhibitor antidepressants (e.g. paroxetine, fluoxetine). Fulvestrant at the dose of 500 mg every 4 weeks has demonstrated superiority compared with anastrozole in the first-line setting [II, A].

Second and further lines of endocrine therapy may include (if not previously used) tamoxifen, steroidal or nonsteroidal AIs, fulvestrant, progestins (e.g. megestrol acetate) and androgens. No definitive recommendation can be given for a specific endocrine treatment cascade, and particularly, the best option after progression on first-line AI therapy is currently unknown.

Recent evidence suggests that the addition of the m-TOR inhibitor everolimus to either a steroidal AI or tamoxifen may improve outcome, compared with endocrine therapy alone, in patients progressing on/after AI therapy but additional research is needed to clearly identify those patients who may benefit from this approach. Additionally, everolimus is not yet approved by the European Medicines Agency (EMA) or United States Food & Drug Administration (FDA) although it has been approved in some countries.

Patients with clear evidence of endocrine resistance should be offered chemotherapy. No overall recommendation can be made regarding the number of lines of endocrine therapy before switching to chemotherapy. Factors that need to be taken into account in this treatment decision include response to previous endocrine therapies and its duration, presence of symptoms and/or rapidly progressive or life-threatening disease, patient preference and performance status, as well as the estimated tolerability of chemotherapy (Figure 3).

'triple-negative' breast cancer (hormonereceptor-negative and HER-2-non-overexpressed/non-amplified)

Cytotoxic chemotherapy remains the mainstay of treatment in this group. Available agents/regimens are listed in Table 4.

The selection of the best agent/regimen should be individualized and should take into account the factors listed in Table 2. Taxane-based regimens are the only standard of care in first-line therapy in patients progressing after adjuvant anthracycline-based non-taxane-containing chemotherapy regimens [I, A].

Because of frequent visceral involvement, aggressive course and risk of rapid patient deterioration, combination

Table 4. Available chemotherapy agents/regimens for MBC

Anthracycline-containing
Doxorubicin or epirubicin monotherapy (weekly or tri-weekly)
Doxorubicin/cyclophosphamide or epirubicin/cyclophosphamide
Liposomal doxorubicin ± cyclophosphamide
Fluorouracil/doxorubicin/cyclophosphamide or fluorouracil/epirubicin/cyclophosphamide
Taxane-containing
Paclitaxel monotherapy weekly
Docetaxel monotherapy tri-weekly or weekly
Abraxane (nab-paclitaxel)
Anthracycline (doxorubicin or epirubicin)/taxane (paclitaxel or docetaxel)
Docetaxel/capecitabine
Paclitaxel/gemcitabine
Paclitaxel/vinorelbine
Paclitaxel/carboplatin
New cytotoxic agents
Eribulin
Ixabepilone (not approved by EMA)
Non-anthracycline-containing
Cyclophosphamide/methotrexate/fluorouracil (CMF)
Platinum-based combinations (e.g. cisplatinum + 5-fluorouracil; carboplatin + gemcitabine)
Capecitabine
Vinorelbine
Capecitabine + vinorelbine
Vinorelbine ± gemcitabine
Oral cyclophosphamide with or without methotrexate (metronomic chemotherapy)

chemotherapy is more often required. Triple-negative biology on its own, however, is not a sufficient reason to give combination chemotherapy. There is no standard approach for patients requiring second- or further-line chemotherapy treatment.

Duration of each regimen and number of regimens should be tailored to each individual patient. Continuing chemotherapy beyond third-line may be justified in patients with good performance status and response to previous chemotherapy.

High-dose chemotherapy with stem cell support should not be administered.

HER-2-positive (overexpressed/amplified) breast cancer

Anti-HER-2 therapy (i.e. trastuzumab, lapatinib) in combination with chemotherapy, endocrine therapy or alone should be offered early to all HER-2-positive MBC patients [I, A] who do not have contra-indications for these therapies.

Addition of pertuzumab to first-line chemotherapy–trastuzumab combination was associated with improved response rate, progression-free survival (PFS) and a trend toward improved overall survival in one randomized phase 3 trial. The patient population of this trial cannot, however, be considered representative of the majority of first-line ABC patients since patients had received little adjuvant therapies (90% did not receive adjuvant trastuzumab and ~50% did not receive adjuvant anthracycline/taxane-based chemotherapy). The added value of this approach, its cost-effectiveness and predictive biomarkers of response should be further evaluated. Pertuzumab has recently been approved by the FDA and a decision is awaited by the EMA.

Cytotoxic-antibody conjugate T-DM1 has demonstrated superior efficacy regarding PFS and a more favorable toxicity profile, when compared with the first-line docetaxel–trastuzumab combination. T-DM1 is not yet approved by the EMA or FDA.

Continuing trastuzumab, in combination with a different chemotherapy regimen, after the first disease progression is superior to chemotherapy alone [II, B]. The benefit of continuing anti-HER-2 therapy beyond first progression is based on less data but available evidence suggests to continue anti-HER-2 therapy for as long as possible.

Lapatinib in combination with capecitabine, compared with capecitabine alone, increases time to progression in patients progressing after/on trastuzumab, anthracyclines or taxanes. The question of continuing trastuzumab or changing to lapatinib at the time of first progression remains open.

The combination of trastuzumab and lapatinib seems to be superior in terms of overall survival to lapatinib monotherapy in patients progressing after/on anthracyclines, taxanes or trastuzumab (not yet approved).

The addition of anti-HER-2 agents (trastuzumab or lapatinib) to endocrine therapy allows for prolongation of PFS and may be a viable option for some patients with ER/PR-positive and HER-2-positive tumors, in particular in those not considered for cytotoxic chemotherapy. In countries where anti-HER-2 treatment is reimbursed only with a single therapy treatment line, priority should be given to an anti-HER-2 + chemotherapy combination, as it may enable a more rapid and potentially more durable response (expert opinion).

other biological agents

- Bevacizumab, an anti-angiogenic agent, originally approved by the FDA and the EMA for first-line treatment of MBC, failed to consistently demonstrate clinically relevant improvement in PFS and has not improved overall survival. For this reason and because of an unfavorable efficacy–safety profile, the FDA revoked its conditional approval in 2011. In Europe, bevacizumab remains approved, only as first-line therapy in combination with paclitaxel or capecitabine. It may thus be considered in carefully selected patients with limited treatment options, requiring a well thought out balance between side-effects, benefits and costs.

response evaluation

Response evaluation is routinely recommended every 2 to 4 months of endocrine therapy and every two or four cycles of chemotherapy by clinical examination, evaluation of symptoms, blood tests (including tumor markers if initially elevated) and repeating the initially abnormal radiological examinations with comparative measurements. The main aim

of these assessments is to exclude progressive disease, in particular in patients for whom further treatment options exist or those who experience significant toxic effects from their treatment. The interval between assessments should be tailored to the clinical needs of the patient and to the aggressiveness of the disease and may be prolonged in case of indolent disease and long-lasting responses. In case of clinical suspicion of progressive disease, appropriate tests (imaging and laboratory) should be carried out irrespective of scheduled examinations, if necessary including areas not imaged in previous tests.

Bone scans should be used with caution and only if other imaging tests are unavailable to solely assess response in bone due to the risk of a flare response being confused with progression.

Serum tumor markers (such as CA 15-3 and/or CEA), if initially elevated, may be helpful in monitoring response, particularly in the case of non-measurable disease. However, a change in tumor markers alone should not be used as the only determinant for treatment decisions. Additionally, it is not uncommon for a phenomenon of flare of tumor markers to occur in the first 6 weeks of an efficacious therapy and this must be taken into account when interpreting serial values.

The role of PET/PET–CT in response assessment is still under investigation but it may be used to determine disease progression.

Maintenance of a good quality of life is paramount and can best be achieved with prompt amelioration of symptoms and side-effects of treatment. Psychometrically sound, well-validated questionnaires are available to measure patient reported outcomes. Efforts should be made to use them regularly to help assess the impact of treatment and to monitor symptoms that need prompt supportive intervention.

follow-up

Follow-up after curative treatment of local–regional recurrence should be carried out as for primary breast cancer.

Patients with MBC must be seen frequently enough to provide best possible palliation of symptoms and maintain quality of life, which generally means every 2–4 months if on endocrine therapy and every one or two cycles of chemotherapy (with toxic effects and blood counts checked before each chemotherapy cycle). If progression is suspected (due to aggravation or appearance of new signs/symptoms and/or significant increase in tumor marker levels), response evaluation should be done immediately.

There is no defined optimal visit schedule for MBC patients in disease remission with no active treatment; however, apart from scheduled visits, these patients should be instructed to contact their physician immediately in case of symptoms suggestive of progressive disease or treatment complications.

Patients need good quality information and a care plan outlining all aspects of treatment and care, clarification of the purpose of different treatments, their side-effects and potential impact on functional, emotional and social well-being.

Lifelong access to effective palliative care is mandatory.

Table 5. Summary of recommendations for management of metastatic breast cancer

The management of metastatic breast cancer should involve all appropriate specialties in a multi/interdisciplinary team
From the first diagnosis of metastatic breast cancer, patients should be offered personalized appropriate psychosocial, supportive and symptom-related interventions as a routine part of their care
Following thorough assessment and confirmation of metastatic breast cancer, the realistic treatment goals must be specified and discussed. Patients and caregivers (if patient agrees) should be invited to participate in decision making
An aggressive multidisciplinary approach including local therapy may be warranted in selected patients with limited metastatic disease
Minimal staging work-up for metastatic breast cancer includes a history and physical examination, complete hematology and biochemistry, imaging of chest, abdomen and bone. The clinical value of tumor markers is not well established for diagnosis or follow-up; however, their use for monitoring response to treatment, particularly in patients with non-measurable disease, is useful
Treatment choice should take into account tumor biology and disease burden, previous therapies and responses obtained, patient preferences, performance status and co-morbidities, socio-economic, psychological factors and therapies available in the patient's country
Endocrine therapy is the preferred option for hormone receptor-positive disease, unless rapid response is warranted or endocrine resistance is suspected
HER-2-directed therapy should be offered early to all HER-2-positive metastatic breast cancer patients, either as single agent, combined with chemo- or with endocrine therapy. Patients progressing on an anti-HER-2 therapy combined with a cytotoxic agent should be offered a second line of anti-HER-2 therapy
Sequential mono-chemotherapy is the preferred option in metastatic breast cancer in the absence of rapid clinical progression, life-threatening visceral metastases or the need for rapid symptom and/or disease control
There are only a few proven standards of care in metastatic breast cancer management, and inclusion of patients in well-designed, independent, prospective randomized trials must be a priority
In view of rising costs of metastatic breast cancer treatment, balanced decisions should be made but patient well-being, length and quality of life must always be the main decision factors
Validated patient reported outcome measures provide useful information about symptom severity and the burden and the impact of these symptoms on overall quality of life, and should be collected and integrated with other clinical assessments, to form part of the treatment decision making

note

Table 5 summarizes the recommendations for the management of MBC. Levels of evidence [I–V] and grades of recommendation [A–E] as used by the European Society for Medical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

The authors have declared no potential conflicts of interest.

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