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

SUPPLEMENTARY TEXT

Section 1. Diagnosis, pathology and molecular biology

In addition to oestrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2), the following biomarkers are linked to the use of approved drugs and should therefore be assessed as part of routine clinical practice [see European Society for Medical Oncology (ESMO) scale for clinical actionability of molecular targets (ESCAT) for further details – **supplementary Table S1**]:

- Germline *BRCA1/2* mutation (*gBRCAm*) testing to guide therapy [i.e. the use of platinum chemotherapy (ChT) and poly (ADP-ribose) polymerase (PARP) inhibitors, where available], with optional *partner and localiser of BRCA2 (PALB2)* mutations and somatic *BRCA* mutations testing [I, A; ESCAT score: I-A].[1] Research indicates that the majority of *BRCA* germline variants can be identified by somatic tumour sequencing [II, A].
- Programmed death-ligand 1 (PD-L1) by immunohistochemistry (IHC) in metastatic triple negative breast cancer (mTNBC). The use of companion assays and scoring systems, i.e. antibody SP142 (Ventana) immune cells score (IC) ≥1% or antibody 22C3 (Dako) combined positive score (CPS) ≥10, are required to select first-line treatment with atezolizumab plus nab-paclitaxel or pembrolizumab plus chemotherapy (ChT) in patients with mTNBC [I, A; ESCAT score: I-A]. The positivity rate may vary according to tissue origin (primary versus site of metastasis) – liver metastases are known to have low PD-L1 expression.[2] Reassessment in another tissue site may therefore be needed in such cases, although caution should be taken interpreting results from decalcified bone samples.[3]
- *Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)* mutations in ER-positive, HER2-negative breast cancer (BC) [I, A; ESCAT score: I-A].

Genomic profiling and further tests on the tumour should be performed as part of routine clinical practice if the result will change the treatment approach, as guided by the ESCAT scale tier I (see **supplementary Table S1**). Where corresponding therapies are available as a treatment option, the following should be tested:

- Microsatellite instability (MSI) by IHC or a validated PCR or sequencing method [III, A; ESCAT score: I-C].
- Tumour mutation burden (TMB)-high by a validated sequencing method [III, B]
- *Neurotrophic tyrosine receptor kinase (NTRK)* screening by IHC, with confirmation by fluorescence *in situ* hybridisation (FISH) or next-generation sequencing (NGS) of DNA or RNA, at least if there is suspicion of secretory BC. This is optional for all other tumour types given the rarity of *NTRK* fusions [III, A; ESCAT score: I-C].

There are additional markers that have the potential to guide therapy, although assessment is optional (see **supplementary Table S1**):

- *Oestrogen receptor 1 (ESR1)* mutation testing if second-line aromatase inhibitor (AI) therapy is being considered [I, B; ESCAT score: II-A].
- *BRCA* tumoural status is optional as *gBRCAm* status is required for the treatment indication. Nevertheless, testing on the tumour to identify somatic mutations may identify treatment options [III, B; ESCAT score: II-A].
- Research testing for *HER2* and *AKT1* mutations and HER2-low status by IHC [ESCAT score: II-B] (see new drugs section).

There are additional markers that should not be measured due to a lack of evidence for clinical consequences in metastatic breast cancer (MBC):

- Ki67 testing is not recommended [I, D].[4]
- Tumour-infiltrating lymphocytes (TILs) assessment is not recommended [I, D] unless in the setting of concurrent PD-L1 evaluation.[5]
- There is evidence that patients with ER-positive, HER2-negative BC and *retinoblastoma tumour-suppressor gene (RB1)* loss-of-function mutations or basal-like gene expression profile may not benefit from CDK4/6 inhibitors. However, testing *RB1* is not routinely recommended [III, C].

Current evidence suggests that both tissue biopsy and circulating tumour DNA (ctDNA) assays can be used to test for *PIK3CA* mutations and MSI status. ctDNA assays vary in sensitivity and some give false negative results; a tissue biopsy may therefore be needed to confirm a negative ctDNA result.[6,7]

Section 2. Triple-negative breast cancer definitions

Recently, triple-negative breast cancers (TNBCs) have been subdivided into six subtypes including two basal-like (BL1 and BL2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem-like (MSL) and a luminal androgen receptor (LAR) subtype.[8] Among these, certain subtypes are associated with a probability of response to specific treatments such as antiandrogens for LAR. *BRCA* mutations are more common in the BL1 subtype and, in general, the prevalence of *gBRCAm* is much higher in women with TNBC referred for genetic counselling.[9] In addition, the new definition of a HER2-low population, which may benefit from certain anti-HER2 treatments,[10] could also be considered soon. It is estimated that nearly a third of TNBCs have a HER2-low status.[11] Finally, treatments targeting the tumour environment such as immune checkpoint Inhibitors (ICIs) or antiangiogenic drugs have been preferentially studied or used in TNBC due to the initial absence of targeted treatments specific to these cancers. The establishment of guidelines for the management of TNBC therefore requires, on the one hand, a global approach in the absence of theragnostic factors and, on the other hand, the individualisation of strategies specific to the populations that may benefit from specific treatments.

Section 3. Hereditary BC (*gBRCAm*)

A small study suggests that PARP inhibitors are efficacious in patients with germline *PALB2* alterations or in tumours that harbour somatic *BRCA* alterations.[1] There are theoretical reasons that breast and ovarian cancers associated with RAD51C or RAD51D will also respond, although there are so far no clinical data demonstrating this.[12]

Criteria that have been used to determine eligibility for g*BRCAm* testing were designed to counsel patients in the setting of hereditary BC rather than for use as a predictive factor in the setting of therapy selection. Studies suggest that these criteria

are imperfectly sensitive for the detection of pathogenic/likely pathogenic alterations. For example, in a hospital-based series of 3,907 women with BC, the United States (US) National Comprehensive Cancer Network (NCCN) criteria for genetic testing were only 87% sensitive for the detection of *gBRCAm*.[13] When evaluating women for a therapeutic option such as PARP inhibition, criteria-based testing risks unacceptable misclassification and failure to identify patients who may benefit from a PARP inhibitor. Expanding criteria to allow testing of all women diagnosed with BC at or before the age of 65 raised the sensitivity to 98%.[13] However, expanding access to testing will require broader access to and modification of existing pre-test counselling models and test turn-around times to accommodate time-sensitive treatment decision-making.

Section 4. Site-specific management

Locoregional breast surgery in patients diagnosed with primary stage IV disease. The incidence of newly diagnosed BC patients presenting with stage IV disease with an intact primary tumour is as high as 20% in some settings. The role of locoregional therapy (LRT) in this situation is still unclear. Four randomised controlled trials (RCTs) addressed this question, collectively including almost 1000 patients.[14-17] However, none of these RCTs stratified patients according to tumour burden or subtype, nor did they mandate metastatic biopsy to verify diagnosis. Two RCTs excluded patients who progressed on systemic therapy,[14,16] but in two trials,[15,17] randomisation was performed at initial presentation. Patients with bone-only disease represented 20%-50% of the population. Surgery performed in the LRT groups was mastectomy in >70% of patients.

None of the trials met their primary survival endpoint [overall survival (OS) or 3-year OS], but with longer follow-up (5 years), in the Soran et al trial,[17] an OS benefit was detected for LRT [42% LRT versus 24% systemic therapy, hazard ratio (HR) 0.66; *P* = 0.005]. An unplanned subgroup analysis also showed better OS in the LRT group for hormone receptor (HR)-positive tumours, HER2-negative tumours, age <55 years and patients with bone-only solitary metastasis. In contrast, all trials showed a clear benefit in time to locoregional progression in patients treated with LRT. The impact of treatment on health-related quality of life (HRQoL) in the trials

that reported this endpoint[15,16] did not differ between patients in either group since an improvement was seen for all patients treated for their disease.

Systemic therapy was not optimal in most studies, resulting in a wide range of median OS reported from 19 months[14] to 54 months,[16] and in one study,[14] only 5% of patients received taxanes and 92% of HER2-positive patients did not receive anti-HER2 therapy, which would impact prognosis of these patients. Other relevant limitations are that some patients randomised to systemic therapy received LRT as palliative therapy for locoregional progression, and none of the trials considered surgery or stereotactic body radiotherapy (SBRT) for oligometastatic disease (OMD).

The ongoing JCOG1017 PRIM-BC[18] and future trials considering optimal systemic therapies and local therapies with a curative intent in OMD may add evidence regarding how to better manage patients with an intact primary tumour diagnosed with stage IV BC.

OMD. A proportion of patients with MBC may present or recur with limited metastatic disease, referred to as OMD. Various definitions of OMD have been proposed based on the number and/or size of the metastatic lesions.[19-21] The patient may have up to five lesions in total, not necessarily in the same site/organ. Importantly, all lesions should be potentially amenable to local treatment.

The clinical challenge in these scenarios is whether treatment should follow a ***palliative*** approach or be escalated to pursue complete and sustained remission (***curative*** approach).

In most cases, multimodality approaches involving local therapy or LRT [high conformal radiotherapy (RT), image guided ablation such as radiofrequency ablation (RFA), selective internal radiotherapy (SIRT) and/or surgery] combined with systemic treatments are tailored to the disease presentation in the individual patient [V, C]. Some subtypes of BC may be very sensitive to systemic treatment. Thus, although the ideal therapy sequence has not been defined, it seems reasonable to document tumour response with systemic treatment before suggesting localised RT or surgery [V, C].

There are no definitive data from randomised trials regarding the best management of OMD.[22] However, these patients need to be discussed in a multidisciplinary context in order to define the best approach [V, C].

Bone metastases. Bone metastases are a common clinical problem, affecting up to 70% of patients with MBC, and are associated with significant morbidity and frequently compromise QoL.[23] A multidisciplinary supportive approach is essential to manage patients with bone metastases and prevent skeletal-related events (SREs) [V, A].

Appropriate diagnostic imaging [i.e. computed tomography (CT) for fracture risk and magnetic resonance imaging (MRI) for suspected cord compression] is recommended to define the extent of disease and the risk of fractures depending on the structural damage and the specific metastatic site. An orthopaedic evaluation is advised in case of significant lesions in long bones or vertebrae as well as in patients with metastatic spinal cord compression (MSCC) to discuss the possible role of surgery [IV, A].

RT is indicated for lesions at moderate risk of fracture and those associated with moderate to severe pain [I, A]. A single 8 Gy fraction has been shown to be as effective as fractionated schemes in uncomplicated metastases [I, A].[24] However, a recent RCT demonstrated superior and more prolonged pain response rates in patients treated with 24 Gy in two daily fractions delivered via SBRT.[25] RT should be delivered after surgery for stabilisation or separation surgery for MSCC [III, B].

Systemic treatment should follow general principles of managing MBC according to subtype.

Bone modifying agents (BMAs, e.g. bisphosphonates or denosumab) are recommended for all patients with bone metastases whether symptomatic or not [I, A].[26,27] In patients treated with zoledronate, it is safe and effective when administered every 12 weeks in cases of stable disease after 3-6 monthly treatments [I, B]. Denosumab is a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor that can be administered subcutaneously. It should be administered every 4 weeks and has been shown to be more effective than zoledronate in delaying first and subsequent SREs [I, B].[26] There is no efficacy data for other intervals besides

monthly treatment. From a health economics perspective, bisphosphonates are considered more cost effective [III, B].[28] For patients progressing on a BMA, it is unclear if changing to another agent with a different mechanism of action is of benefit. In patients progressing on intravenous bisphosphonates, denosumab could be an alternative since it has shown some benefit in a small phase II trial.[29]

Before initiation of BMA therapy, patients should have a complete dental evaluation and ideally complete any required dental treatment.[30] Concomitant calcium and vitamin D supplementation should be recommended to all patients using these agents [III, A].

The optimal duration of BMA therapy has not been defined but interruption after 2 years may be discussed for patients in remission [II, B].[30]

Brain metastases. BC is the second leading cause of brain metastases (BMs).[31] The median OS of patients with BMs is 2-16 months depending on involvement of the central nervous system (CNS), the extent of the extracranial metastatic disease and the treatment applied.[32] The presence of BMs should be explored by brain imaging in all patients who present with clinical signs or symptoms of raised intracranial pressure, seizures or new neurological deficits. In mTNBC or HER2-positive MBC, brain imaging could be considered in asymptomatic patients based on the high probability of BMs in these subtypes, even as the first site of metastasis, if detection of CNS metastases will alter the choice of systemic therapy [V, C].[33,34] The diagnostic work-up of patients with suspected BMs, as a minimum, should include cranial MRI. If MRI is not available, a contrast CT scan can be performed. Patients with a single BM should be considered for surgery whenever possible; stereotactic radiosurgery (SRS) is recommended for patients with a limited number (1-4) of BMs [I, A]. However, SRS may be considered even for patients with a higher number of BMs (4-10) provided the cumulative tumour volume is <15 mL [II, B].[35] Whole brain radiotherapy (WBRT) should be considered in case of multiple BMs [III, B]. The use of systemic therapy should consider molecular subtype and CNS efficacy. In HER2-positive MBC, the use of anti-HER2 therapies may be considered in patients not requiring immediate local therapy [II, B]. Tucatinib (together with trastuzumab and capecitabine) yielded a significant OS improvement even in patients with active BMs

in the HER2CLIMB trial.[36] The use of intrathecal trastuzumab remains investigational.[37] In patients with HER2-negative BC, ChT may be considered [III, B]. This topic has been reviewed extensively in the recent European Association of Neuro-Oncology (EANO)-ESMO Clinical Practice Guideline (CPG) on the management of patients with BMs from solid tumours.[35]

Local treatment for asymptomatic CNS disease remains controversial and upfront systemic therapy may also be an option for these patients depending on the tumour subtype.

Leptomeningeal metastases. BC, lung cancer and melanoma represent the three most common causes of leptomeningeal metastases (LMs).[38] Patients with lobular subtype or triple-negative tumours have a relatively higher risk of LMs than patients with other subtypes.[39] Median OS is poor and limited to 1.75-4.5 months in MBC.

Three agents are commonly used for intrathecal treatment of LMs: methotrexate (MTX), cytarabine (ara-C), including liposomal ara-C, or thiotepa, but they have not demonstrated improvements in OS. RT should be considered for patients with symptomatic LMs, either as localised RT for nodular lesions or as WBRT for extensive nodular or linear LMs. Recommendations for treatment are well described in the EANO-ESMO CPG for the management of patients with LMs from solid tumours.[38] In MBC, new agents with documented CNS efficacy may also constitute systemic therapy options.[40,41]

Section 5. New drugs

Despite progress in treating MBC, the disease remains incurable and effective treatment options are limited for some patient populations. For example, in patients with mTNBC, 5-year survival rates for distant disease remain low at approximately 11% in the US.[42] ChT response rates range from approximately 15%-20%, with a median progression-free survival (PFS) of only 2-3 months. Less than 50% of patients qualify for currently approved targeted agents or immunotherapy, with approximately 10%-20% of patients harbouring *gBRCAm* and 40%-50% having a positive PD-L1 status or a TMB >10. As such, there is an ongoing need for new agents and strategies in this area. Drug development has led to recent advances in

antibody-drug conjugates (ADCs), immunotherapy and targeted therapies, and several drugs have received license approval in MBC in the US and/or in Europe over the past 2 years, with future approvals anticipated throughout the rest of the world.

A number of ADCs, utilising a variety of antibodies, linkers and chemotherapeutics for a variety of BC subtypes, have entered the clinical trial pipeline; patients should be encouraged to participate in these trials.

Sacituzumab govitecan-hziy [sacituzumab; Food and Drug Administration (FDA)-approved, not European Medicines Agency (EMA)-approved] is an ADC comprising a humanised anti-Trop2 antibody, a hydrolysable linker and a payload consisting of DNA-38, a metabolite of irinotecan. Trop2 is an epithelial antigen expressed on many solid tumours; however, initial data suggest that measurable expression of the antigen on TNBC cells is not essential for activity.[43] The linker has been optimised to enable a high drug—antibody ratio of 7.6:1 which, along with its hydrolysable nature, is thought to enable both high direct payload delivery and a bystander effect. Accelerated FDA approval for sacituzumab was based on a single arm, phase I/II dose escalation, dose expansion study (IMMU-132-01), which enrolled patients with breast, urothelial, lung and other cancers in the phase II part of the study.[44] Regular approval was granted by the FDA based on results of ASCENT, a phase III confirmatory trial that randomised the same mTNBC population (i.e. >2 prior lines of ChT) to sacituzumab 10 mg/kg on day 1 and 8 q3w versus treatment of physician's choice (TPC), with options including eribulin, vinorelbine, gemcitabine or capecitabine.[45] Sacituzumab has also been explored in metastatic HR-positive BC, and among 54 patients who had received at least one line of ChT for metastatic disease, response rate (RR) was 31.5% [95% confidence interval (CI) 19.5%-45.6%], and median PFS was 5.5 months (95% CI 3.6-7.6).[46] These data led to the randomised phase III trial, TROPICS-02, which randomised patients with metastatic HR-positive, HER2-negative BC to sacituzumab or TPC.[47]

Another area of rapid new drug development is in the setting of HER2-positive MBC. Here, three new agents have been approved by the US FDA and two by the EMA over the past 2 years: fam-trastuzumab deruxtecan-nxki (trastuzumab deruxtecan), tucatinib (FDA-approved, not EMA-approved) and margetuximab-cmkb (margetuximab; FDA-approved, not EMA-approved). Trastuzumab deruxtecan is an

ADC that is comprised of a HER2-directed monoclonal antibody, an enzyme-cleavable linker and a novel topoisomerase I inhibitor payload. Trastuzumab deruxtecan received accelerated FDA approval in December 2019 based on the DESTINY-Breast01 trial for HER2-positive MBC. Data from a phase IB study also suggests that trastuzumab deruxtecan has activity in patients with HER2-low [IHC 1+ or 2+/*in situ* hybridisation (ISH)-negative] BC, with an objective response rate (ORR) of 37% reported among 54 evaluable patients.[48] These data led to a randomised phase III trial comparing trastuzumab deruxtecan with TPC ChT in pretreated patients with metastatic HER2-low BC (NCT04494425).

Section 6. Side effects

Management of common toxicities

Fatigue is the most common side effect of BC treatment. It can appear early in treatment, be overwhelming and is not eased by rest. Contributing factors should be considered, including concomitant medications, anaemia and progressive disease. The recommended management of fatigue includes a dose reduction of current treatment and physical activity with intermittent rest periods.[49]

Nausea and vomiting are common side effects of many therapies. Principles of management include both prophylaxis and rescue medications. Newer therapies, such as 5-HT3 antagonists, substance P/neurokinin 1 (NK1) receptor antagonists, and the antipsychotic olanzapine added to standard medications such as dexamethasone, have greatly improvement symptom control.[50,51]

Bone marrow suppression, including neutropaenia, anaemia and less commonly, thrombocytopenia, occur with the majority of therapies used to treat BC. Management generally includes myeloid growth factors, transfusions, dose reduction and delay.[52-54]

Menopausal symptoms, including vasomotor effects, reduced libido and vaginal dryness, are common side effects in younger women that can have a significant impact on quality of life (QoL). These symptoms can be managed with low-dose antidepressants (for hot flushes; interactions with tamoxifen metabolism need to be taken into account) and low-dose vaginal oestrogens with transient

negligible absorption.[55] For decreased libido, two agents are approved, but there are no safety data in women with BC [III, A].

Peripheral sensory neuropathy can occur with several classes of agents used to treat BC. Treatment includes dose reduction, a change in schedule and gabapentin for symptom management. Early studies suggest possible prevention with exercise and functional training as well as with compression and/or cold gloves and socks [IV, A].[56]

Alopecia from many common chemotherapeutic agents may be reduced by scalp cooling; this is agent-, schedule- and dose-dependent [III, A].[57]

Management of therapy-specific toxicities

Targeted therapies are associated with side effects that may be distinct from ChT or endocrine therapy (ET). In general, toxicities must be assessed and managed in the context of the specific drug, as exemplified by neutropaenia induced by CDK4/6 inhibitors versus that by ChT. Some toxicities are off-target effects, exemplified by the side effect profile of ICIs, which can elicit a wide spectrum of immune-related toxicities affecting any organ (skin being the most common), and are distinct from conventional cytotoxics. Adverse events (AEs) can occur early as well as months after last exposure to the drug. Endocrine effects of ICIs can include hyper- or hypothyroidism, adrenal insufficiency and, rarely, diabetes. Close monitoring is therefore essential. Another example is the PIK3CA inhibitor, alpelisib, which is associated with hyperglycaemia and rash. Examples of drug-specific toxicities are shown in **supplementary Table S2**.

Proactive management requires early identification and management, and in some cases prophylaxis.

Section 7. Patient perspective

Patient expectations of treatment and what ‘clinical benefit’ means for patients

Every person facing a diagnosis of MBC does so in their own way but there are great similarities. Throughout MBC treatment, patients receive different drugs and many of them have severe side effects. Patients very often emphasise that QoL is more

important to them than PFS or OS. A healthy person would tend to ask why but a patient with cancer would agree. Hereby, the importance of psychosocial support comes to the forefront.

For all patients with BC, including those with MBC, receiving optimal care as part of a multidisciplinary team (MDT) approach is of greatest importance.

Besides access to optimal treatment, patient information and education is particularly important. Only well-informed and educated patients can be equally involved in treatment choices, leading to improved treatment outcomes.[58] Patient education can be achieved by good communication between the patient and their doctor/MDT. Patients should have access to all information about their treatments in lay language, explained in simple terms.

In the metastatic setting, patients are aware of different options but sometimes differences are not clear, particularly in terms of expectations of a new treatment and how this may improve their lives. A common concern for many patients when starting a new treatment is that they don't want to suffer cancer- and/or treatment-related effects. For every new line of treatment, patients expect disease progression to stop, but not at all costs. Patients want to maintain good QoL, the definition of which can differ from patient to patient depending on personal preferences, cultural and religious perspectives and age. Again, this highlights the need for good communication, with a high level of confidence/trust, as well as professional psychosocial support right from the beginning. This communication and support will also result in better recognition and management of side effects by the patient and improved treatment adherence.

For patients with MBC, it is not just treatment that is important since they are also facing a lot of uncertainty and anxiety regarding their future in terms of what will happen next, how to organise their lives and what additional help they may need in the future. In addition to psychosocial support, patient support groups or on-line closed groups can provide safe places for patients and give them a lot of the emotional support that they need.

Patient perceptions of the ESMO-MCBS

The ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a highly appreciated tool for scoring the clinical benefit of treatments and is simple to use.[59] Given the fact that it is still not well-recognised among patients, patient-directed education regarding the ESMO-MCBS is needed.

Supplementary Table S1. List of targetable alterations of level I/II according to ESCAT in MBC.

Gene or protein	Alteration	Prevalence	ESCAT score[a]
ER	Protein expression ≥ 1% by IHC *ESR1 mutation*	75% 40%	NA II-A
ERBB2[60,61]	Amplifications or 3+ by IHC HER2-low status by IHC (1+, 2+ non amplified)	15%-20% 40%-50%	I-A II-B
	Hotspot mutations	4%	II-B
BRCA1/2[60]	Germline mutations	4%	I-A
	Somatic mutations	3%	II-A
PALB2[61]	Germline mutations	1%	II-A
PD-L1 (TNBC)[2]	Expression by IHC on Immune cells (ic) and tumour cells (CPS)	40%	I-A
PIK3CA (ER-positive, HER2-negative)[60]	Hotspot mutations	30%-40%	I-A
MSI[60]	MSI-H	1%-2%	I-C
NTRK[60]	Fusions	<0.1%	I-C
ESR1 (ER-positive, HER2-negative)	Mutations (mechanism of resistance)	30%	II-A
AR (TNBC)	AR expression (testing and cut-off not validated)	?	II-B
AKT1^{E17K} [60,61]	Mutations	5%	II-B

AR, androgen receptor; CPS, combined positive score; ER, oestrogen receptor; *ERBB2, Erb-B2 receptor tyrosine kinase 2*; ESCAT, ESMO scale for clinical actionability of molecular targets; *ESR1, oestrogen receptor 1*; HER2, human epidermal growth factor receptor 2; ic, immune cells; IHC, immunohistochemistry; MBC, metastatic breast cancer; MSI, microsatellite instability; MSI-H, microsatellite

instability high; NA, not available; *NTRK, neurotrophic tyrosine receptor kinase*; *PALB2, partner and localiser of BRCA2*; PD-L1, programmed death-ligand 1; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TNBC, triple-negative breast cancer.

[a] ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[62]

Supplementary Table S2. Drug-specific toxicities and associated management strategies

Toxicity	Agent	Management	LoE, GoR
Diarrhoea	Neratinib,[63] lapatinib, pertuzumab, abemaciclib, alpelisib, everolimus	• Dose escalation (neratinib) • Antipropulsives, dietary adjustment and dose reduction/delay	III, B (neratinib)
LVEF decline	Trastuzumab, pertuzumab, HER2-targeted oral TKIs and ADCs[64]	• Monitor EF at baseline and hold therapy in cases where EF is below normal range • Monitor cardiac function throughout therapy • For trastuzumab, data suggests that concomitant cardiac medications (ACE inhibitors or beta blockers) can reduce cardiac toxicity	I, A/B
Hyperglycaemia	Alpelisib	• Hyperglycaemia occurs early (within 1-3 weeks) and can be severe • Screen for risk with HbA1c and fasting glucose • Monitor closely every week for the first 4 weeks of therapy • Early initiation of hypoglycaemic agents and endocrine consultation	I, A/B
Rash	Alpelisib[65], everolimus	• Rash occurs early (within the first 2-3 weeks of starting therapy)	IV, A/B

		• Prophylaxis with non-sedating antihistamines starting before initiation of alpelisib • Treatment with topical or systemic steroids, as indicated	
Immunotoxicity	PD-L1 and PD-1 antibodies (ICIs)	• Endocrine toxicity: hormone deficiency should be promptly replaced. In general, no adjustment to ICI therapy is needed • Other: any organ can be affected. ICI therapy should be held for grade 2 or 3 toxicity depending on the affected organ. Steroids should be promptly initiated, with specialist consultation. It is not clear in which cases it is safe to restart ICI therapy; this should only be considered when the severity of the toxicity has reduced to grade ≤1 • Early suspicion/identification of toxicity, work-up and treatment is critical • Some of these toxicities may occur after stopping ICI treatment	I, A
QTc prolongation	Ribociclib[66]	• Monitor ECG QTcF interval at baseline then every 2 weeks for the following 4 weeks for QTcF <450 ms	II, B

		• Do not combine ribociclib with agents that are known to prolong QTcF, including tamoxifen	
Mucositis	Everolimus[67]	• Mouthwash (e.g. steroid-containing) used prophylactically to swish, hold and spit five times per day during the first 8 weeks of therapy markedly decreases the incidence and severity of stomatitis	II, A
Liver enzyme elevation	Ribociclib, abemaciclib, tucatinib	• Liver enzymes should be monitored regularly during treatment • Drugs should be held for a grade 3 elevation in liver enzymes and dose reduction should be considered	
Pneumonitis (ILD)	Trastuzumab deruxtecan,[68] atezolizumab, pembrolizumab, everolimus, abemaciclib, palbociclib, ribociclib	• Inflammation of the lung can occur with various different targeted agents, with a highly variable incidence rate from common to extremely rare • Strict guidelines for monitoring, treatment interruption (even for asymptomatic grade 1 pneumonitis) and early institution of steroids has been recommended for trastuzumab deruxtecan, where pneumonitis-related mortality has been observed	

ACE, angiotensin-converting enzyme; ADC, antibody-drug conjugate; ECG, electrocardiogram; EF, ejection fraction; GoR, grade of recommendation; HbA1c, haemoglobin A1C; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; ILD, interstitial lung disease; LoE, level of evidence; LVEF, left ventricular ejection fraction; PD-1, programmed cell death protein 1;

PD-L1, programmed death-ligand 1; QTc, corrected QT interval; QTcF, QT interval corrected using Fridericia's formula; TKI, tyrosine kinase inhibitor

Supplementary Table S3. Randomised clinical trials of ICIs in mTNBC

Study Name Population	Design	N	Median follow-up, months (IQR)	Median OS, months (95% CI)	Median PFS, months (95% CI)	ORR, %	Remarks
Monotherapy trials							
KEYNOTE-119[69] Previously treated mTNBC	ChT[a]	310	31.5 (27.8-34.6)	10.8 (9.1-12.6)	3.3 (2.7-4.0)	10.6	• No median OS or PFS benefit with pembrolizumab according to PD-L1 CPS different cut-offs • Better ORR for pembrolizumab (17.7%) versus ChT (9.2%) in PD-L1 CPS ≥10 population (*P* = 0.04)
	Pembrolizumab	312	31·4 (27.8-34.4)	9·9 (8.3-11.4)	2.1 (2.0-2.1)	9.6	
SAFIR02-BREAST IMMUNO trial[70]	ChT	35	19.7 (16.5-22.3)	14.0 (9.5-16.1)	NR in TNBC subgroup	NA	• No PFS benefit reported in mTNBC subgroup exploratory analysis: unadjusted
	Durvalumab	47		21.2 (16.6-27.3)			

Maintenance therapy in HER2-negative MBC							HR 0.54 (95% CI 0.30-0.97); log-rank test *P* = 0.0377
Combination therapy trials							
IMpassion130[71] First-line treatment of locally advanced unresectable or mTNBC	Nab-paclitaxel + placebo	451	17.5 (8.4-22.4)	18.0 (13.6-20.1)	5.0 (3.8-5.6)	42.6	• Results shown are in PD-L1-positive patients using SP142 • Improved median PFS: HR 0.62 (95%CI 0.49-0.78), log-rank test *P* < 0.001 • Improved median OS (exploratory analysis): HR 0.71 (95%CI 0.54-0.94)
	Nab-paclitaxel + atezolizumab	451	18.5 (9.6-22.8)	25.0 (19.6-30.7)	7.5 (6.7-9.2)	52.9	
IMpassion131[72] First-line treatment of locally advanced	Paclitaxel + placebo	220	8.6 (0.0-26.1)	28.3 (19.1-NE)	5.7 (CI 5.4-7.2)	55	• Results shown are in PD-L1-positive patients using SP142
	Paclitaxel + atezolizumab	431	9.0 (0.5-25.4)	22.1 (19.2-30.5)	6.0 (5.6-7.4)	63	

unresectable or mTNBC							• No median OS or PFS benefit observed with atezolizumab
KEYNOTE-355[73] First-line treatment of locally advanced unresectable or mTNBC	ChT[b] + placebo	281	26.3 (22·7-29·7)	NR	5.6	39.8	• Results shown are in PD-L1 CPS ≥10 • Improved median PFS in PD-L1 CPS ≥10 (primary endpoint): HR 0.65 (95%CI 0.49-0.86); log-rank test *P* = 0·0012 • Median PFS was not different for the overall population or in the PD-L1 CPS ≥1 population
	ChT[b] + pembrolizumab	566	25.9 (22·8-29·9)		9.7	53.2	

ChT, chemotherapy; CI, confidence interval; CPS, combined positive score; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ICI, immune checkpoint inhibitor; IQR, inter-quartile range; MBC, metastatic breast cancer; mTNBC, metastatic triple-

negative breast cancer; N, number; NA, not applicable; NE, not estimable; NR, not reported; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TNBC, triple-negative breast cancer.

[a] Capecitabine, eribulin, gemcitabine or vinorelbine.

[b] Nab-paclitaxel, paclitaxel or gemcitabine plus carboplatin.

Supplementary Table S4. ESMO-MCBS table for relevant therapies/indications in MBC

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score[a]
Abemaciclib + AI	First-line locally advanced or MBC in postmenopausal, hormone receptor-positive, HER2-negative	MONARCH 3[74-76] Phase III NCT02246621	Placebo + AI Median PFS control: 14.8 months	PFS gain: 13.4 months	PFS HR: 0.54 (0.42-0.70)	Not clinically significant	3 (Form 2b)
Abemaciclib + fulvestrant	Second-line locally advanced or MBC in postmenopausal, hormone receptor-positive, HER2-negative	MONARCH 2[77-79] Phase III NCT02107703	Placebo Median PFS: 9.3 months Median OS: 37.3 months	PFS gain: 7.1 months OS gain: 9.4 months	PFS HR: 0.55 (0.45-0.68) OS HR: 0.76 (0.61-0.95)	No QoL benefit observed	4 (Form 2a)

Abemaciclib[e]	Hormone receptor-positive, HER2-negative ABC or MBC with disease progression following ET and prior ChT in the metastatic setting	MONARCH 1[80] Phase II NCT02102490	Single arm	Median PFS: 6.0 months ORR: 19.7% DoR: 8.6 months			3 (Form 3)
Palbociclib + fulvestrant	Hormone receptor-positive, HER2-negative locally advanced or MBC previously treated with ET	PALOMA-3[81-84] Phase III NCT01942135	Fulvestrant + placebo Median PFS: 4.6 months Median OS: 28.0 months	PFS gain: 4.9 months OS gain: 6.9 months	PFS HR: 0.46 (0.36-0.59) OS HR: 0.81 (0.64-1.03) NS	Delayed deterioration of QoL	4 (Form 2b)

Palbociclib + letrozole	First-line postmenopausal, ER-positive, HER2-negative locally advanced MBC	PALOMA-2[85-88] Phase III NCT01740427	Letrozole + placebo Median PFS: 14.5 months	PFS gain: 10.3 months	PFS HR: 0.58 (0.46-0.72)	No QoL benefit	3 (Form 2b)
Ribociclib + ET	First-line premenopausal, hormone receptor-positive, HER2-negative ABC	MONALEESA-7[89-91] Phase III NCT02278120	Placebo + ET Median PFS: 13.0 months Median OS: 40.9 months	PFS gain: 10.8 months OS gain: 16.0 months[b]	PFS HR: 0.55 (0.44-0.69) OS HR: 071 (0.54-0.95)	Delayed deterioration of QoL	5 (Form 2a)
Ribociclib + fulvestrant	First- or second-line postmenopausal, hormone receptor-positive, HER2-negative ABC	MONALEESA-3[92-94] Phase III NCT02422615	Placebo + fulvestrant Median PFS: 12.8 months Median OS: 40.0 months	PFS gain: 7.7 months OS gain: 15.6 months[c]	PFS HR: 0.59 (0.48-0.73) OS HR: 0.72 (0.57-0.92)	No QoL benefit observed	4 (Form 2a)

Ribociclib + letrozole	First-line postmenopausal, hormone receptor-positive, HER2-negative ABC	MONALEESA-2[95-97] Phase III NCT01958021	Placebo + letrozole Median PFS: 16.0 months	PFS gain: 9.3 months	PFS HR: 0.57 (0.46-0.70) No mature OS data	No QoL benefit observed	3 (Form 2b)
Lapatinib + trastuzumab	HER2-positive, hormone receptor-negative MBC after progression on prior trastuzumab + ChT regimen(s)	EGF104900[98,99] Phase III NCT00320385	Lapatinib Median PFS: 8.1 weeks Median OS: 9.5 months	PFS gain: 3.0 weeks OS gain: 4.5 months	PFS HR: 0.74 (0.58-0.94) OS HR: 0.74 (0.57-0.97)		4 (Form 2a)
Pertuzumab + trastuzumab + docetaxel	HER2-positive locally recurrent unresectable or	CLEOPATRA[100-104] Phase III	Placebo + trastuzumab + docetaxel			No improvement in QoL	4 (Form 2a)

	MBC with no prior anti-HER2 therapy or ChT for metastatic disease	NCT00567190	Median PFS: 12.4 months Median OS: 40.8 months	PFS gain: 6.3 months OS gain: 16.3 months	PFS HR: 0.62 (0.52-0.75) OS HR: 0.69 (0.58-0.82)		
T-DM1	HER2-positive, unresectable locally advanced or MBC who previously received trastuzumab and a taxane (extensive crossover)	EMILIA[105,106] Phase III NCT00829166	Lapatinib + capecitabine Median PFS: 6.4 months Median OS: 25.1 months	PFS gain: 3.2 months OS gain: 5.8 months	PFS HR: 0.65 (0.55-0.77) OS HR: 0.68 (0.55-0.85)	Delayed deterioration in QoL	4 (Form 2b)[h]
Margetuximab + ChT[e]	Previously treated HER2-positive MBC	SOPHIA[107] Phase III NCT02492711	Trastuzumab + ChT Median PFS: 4.9 months	PFS gain: 0.9 months	PFS HR: 0.76 (0.59-0.98)		2 (Form 2b)

			Median OS: 19.8 months	OS gain: 1.8 months	OS HR: 0.89 (0.69-1.13) NS interim		
Neratinib + capecitabine[e]	Previously treated HER2-positive advanced or MBC	NALA[108] Phase III NCT01808573	Lapatinib + capecitabine Median PFS: 6.6 months Median OS: 22.2 months	PFS gain: 2.2 months OS gain: 1.8 months	PFS HR: 0.76 (0.63-0.93) OS HR: 0.88 (0.72-1.07) NS	No QoL benefit observed	1 (Form 2b)
Trastuzumab deruxtecan	Patients with unresectable or metastatic HER2-positive BC who have received ≥2 prior anti-HER2-based regimens	DESTINY-Breast01[109] Phase II NCT03248492	Single arm	Median PFS: 16.4 months ORR: 60.9% DoR:14.8 months		52.2% grade ≥3 toxicity 2% toxic fatalities	2 (Form 3)

Tucatinib + trastuzumab + capecitabine[e]	HER2-positive locally advanced or MBC after at least 2 prior anti-HER2 treatment regimes	HER2CLIMB[36] Phase II NCT02614794	Placebo + trastuzumab + capecitabine PFS control: 5.6 months OS control: 17.4 months	PFS gain: 2.2 months OS gain 4.5 months	PFS HR: 0.54 (0.42-0.71)[f] OS HR: 0.66 (0.50-0.88)[g]		3 (Form 2a)
Atezolizumab + nab-paclitaxel[i]	First-line treatment for unresectable locally advanced or metastatic, PD-L1 ≥1% positive TNBC	IMpassion130[71,110,111] Phase III NCT02425891	Placebo + nab-paclitaxel Median PFS (PD-L1-positive): 5.0 months Median OS (PD-L1-positive): 18.0 months	PFS gain: 2.5 months OS gain: 7.0 months	PFS HR 0.62 (0.49-0.78) OS HR: 0.71 (0.54-0.94)[d]	No QoL benefit observed	3 (Form 2b)

Pembrolizumab + ChT[j]	First-line treatment of locally recurrent inoperable or metastatic TNBC PD-L1 (CPS >10)	KEYNOTE-355[112] Phase III NCT02819518	Placebo + ChT Median PFS: 5.6 months	PFS gain: 4.1 months	PFS HR: 0.65 (0.49-0.86)		3 (Form 2b)
Olaparib	Previously treated *BRCA1/2*-mutated, HER2-negative MBC	OlympiAD[113-115] Phase III NCT02000622	Standard ChT (physicians' choice) Median PFS: 4.2 months Median OS: 17.1 months	PFS gain: 2.8 months OS gain: 2.2 months	PFS HR: 0.58 (0.43-0.80) OS HR: 0.90 (0.66-1.23) NS	Delayed deterioration of QoL Reduced toxicity	4 (Form 2b)
Talazoparib	Post anthracycline and taxane in *BRCA1/2*-	EMBRACA[116-119] Phase III	Standard ChT Median PFS: 5.6 months	PFS gain: 3.0 months	PFS HR: 0.54 (0.41-0.71)	QoL improved	4 (Form 2b)

	mutated, HER2-negative ABC	NCT01945775	Median OS: 19.5 months	OS gain: -0.2 months	OS HR: 0.848 (0.670-1.073) NS		
Alpelisib + fulvestrant	Postmenopausal *PIK3CA* mutated, hormone receptor-positive, HER2-negative locally advanced or MBC previously treated with ET	SOLAR-1[65,120-122] Phase III NCT02437318	Placebo + fulvestrant Median PFS: 5.7 months Median OS: 31.4 months	PFS gain: 5.3 months OS gain: 7.9 months	PFS HR: 0.65 (0.50-0.85) OS HR: 0.86 (0.64-1.15) NS	Increased toxicity No QoL benefit observed	2 (Form 2b)
Sacituzumab govitecan-hziy[e]	Patients with unresectable locally advanced or metastatic TNBC who have received	ASCENT[45] Phase III NCT02574455	Physician's choice of single-agent ChT Median PFS: 1.7 months	PFS gain: 3.1 months	PFS HR: 0.43 (0.35-0.54)	Increased toxicity	4 (Form 2a)

	≥2 prior therapies, at least 1 of them for metastatic disease		Median OS: 6.9 months	OS gain: 4.9 months	OS HR: 0.51 (0.41-0.62)		
Bevacizumab + paclitaxel	First-line treatment of patients with MBC	E2100[123] Phase III NCT00028990.	Paclitaxel Median PFS: 5.9 months Median OS: 25.2 months	 PFS gain: 5.9 months OS gain: 1.5 months	 PFS HR: 0.60 (0.51-0.70) OS HR: 0.88 (NS)	 No QoL benefit	2 (Form 2b)
Everolimus + exemestane	Hormone receptor-positive, HER2-negative ABC in combination with exemestane in postmenopausal women	BOLERO-2[124,125] Phase III NCT00863655.	Exemestane + placebo Median PFS: 4.1 months Median OS: 26.6 months	 PFS gain: 6.5 months OS gain: 4.4 months	 PFS HR: 0.36 (0.27-0.47) OS HR: 0.89 (0.73-1.10) NS	No QoL benefit	2 (Form 2b)

	without symptomatic visceral disease after recurrence or progression following a non-steroidal AI						
Larotrectinib	Patients with refractory *NTRK* fusion-positive cancers who are locally advanced, metastatic or where surgical resection is likely to result in severe morbidity and	A study to test the safety of the investigational drug larotrectinib in adults that may treat cancer Phase I NCT02122913 SCOUT Phase I/II NCT02637687	Three single arm trials	ORR: 75% DoR: 9+ months			3 (Form 3)

	who have no satisfactory treatment options	NAVIGATE Phase II adults NCT02576431[126]					
Entrectinib	Patients with solid tumours expressing an *NTRK* gene fusion	STARTRK-1 Phase I NCT02097810 STARTRK-2 Phase II NCT02568267 ALKA-372-001 Phase I EudraCT, 2012–000148–88 STARTRK-NG Phase I/II NCT02650401[127]	Four single arm trials	ORR: 57% DoR: 104 months			3 (Form 3)

ABC, advanced breast cancer; ADC, antibody-drug conjugate; AI, aromatase inhibitor; BC, breast cancer; CI, confidence interval; CHMP, Committee for Medicinal Products for Human Use; ChT, chemotherapy; CPS, combined positive score; DoR, duration of response; EC, European Commission; EMA, European Medicines Agency; ER, oestrogen receptor; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; MBC, metastatic breast cancer; NS, not significant; *NTRK, neurotrophic tyrosine receptor kinase*; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; *PIK3CA*, *phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha*; PE, point estimate; PFS, progression-free survival; QoL, quality of life; T-DM1, ado-trastuzumab emtansine; TNBC, triple-negative breast cancer.

[a] ESMO-MCBS version 1.1[59] was used to calculate scores for new therapies/indications approved by the EMA or the FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1).

[b] Calculated estimate of gain based on PE HR 0.71.

[c] Calculated estimate of gain based on PE HR 0.72.

[d] OS was an exploratory, unplanned *post hoc* analysis not eligible for ESMO-MCBS grading.

[e] FDA-approved, not EMA-approved.

[f] PFS for the first 480 patients randomised.

[g] OS for a total of 612 patients randomised.

[h] Score derived from form 2b criteria with an upgrade for early stopping based on OS advantage detected at interim analysis.

[i] EMA-approved, not FDA-approved.

[j] FDA-approved, CHMP positive opinion September 2021, pending EC decision.

Supplementary Table S5. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

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