

# Systemic Treatment of Patients With Metastatic Breast Cancer: ASCO Resource–Stratified Guideline Q and A

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In 2024, ASCO published a guideline for clinicians, patients, and policymakers in resource-constrained settings on the treatment of patients with metastatic breast cancer (MBC).<sup>1</sup> The purpose of that guideline is to provide expert guidance on the systemic treatment of MBC to clinicians, public health leaders, patients, and policymakers in resource-constrained settings (Appendix Table A1). The guideline's target population is adult patients with MBC in resource-constrained settings and focuses on medical treatment. The guideline is not intended for patients in Maximal settings.

## QUESTION: WHY ARE RESOURCE-STRATIFIED GUIDELINES FOR MANAGEMENT OF PATIENTS WITH MBC NEEDED?

More than half of patients diagnosed with breast cancer worldwide are in regions with limited healthcare resources where access to the most effective treatment may be limited and may vary significantly between healthcare settings and populations. The resource-stratified guidelines aim to address the main challenges of delivering best practice care in the context of such limitations in two ways—first, by providing a framework for healthcare providers that outlines a rational, evidence-based approach to the selection of best treatments in the context of resource limitations (Table 1). Second, these guidelines aim to assist the health systems in identifying the goals for improvement in access to treatments that are the most effective and equitable.

Applying guidelines to the management of patients with MBC presents some unique challenges. Unlike other cancer care interventions that depend on capital infrastructure (such as surgery or screening programs), significant aspects of the management of patients with MBC involve systemic therapies such as hormonal therapy, chemotherapy, or targeted therapy. These agents can be increasingly sourced by patients themselves, and there is significant variation in access that may change rapidly over time, depending on market forces and supply. Accordingly, limitations in resources are not static and require that healthcare providers adopt a flexible, evidence-based, and patient-centered approach.

## QUESTION: WHAT ARE THE MAIN TAKEAWAYS?

The approach to the management of patients with MBC should be guided by the pathological features of the tumor, patients' palliative care needs, and available evidence-based, effective treatment. Within the resource constraints, clinicians should select the most effective accessible treatments with the input of the multidisciplinary care team. Patients' preferences and consideration of any potential financial toxicity need to be considered, especially in settings where the gains in efficacy from costly therapies may be marginal. Research of cancer therapies, including the study of patient-reported outcomes and patients' preferences, conducted in resource-constrained settings should be a priority to build the evidence base.

## QUESTION: WHAT IS THE RECOMMENDED FRONTLINE TREATMENT FOR PATIENTS WITH HORMONE RECEPTOR-POSITIVE MBC?

Hormonal therapy is the cornerstone of management for patients with hormone receptor-positive cancer. The type of hormonal therapy depends on the menopausal status of the patient. For patients who are premenopausal, therapy includes ovarian ablation, either by medical, surgical, or radiation means (see the section on Recommended Treatment for Premenopausal

### ACCOMPANYING CONTENT

 Appendix

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**TABLE 1. Summary of Key Guideline Recommendations**

Recommendation No.	Population	Basic	Limited	Enhanced
HR-positive, HER2-negative				
1.1.1	HR-positive, HER2-negative Postmenopausal	<i>Tamoxifen</i> , palliative, <sup>a</sup> and best supportive care should be provided Surgery and <i>tamoxifen</i> when patient presents with certain symptoms	Sequential hormone therapy <sup>b</sup> Aromatase inhibitors (AIs) only if ovarian ablation/ovarian suppression (OA/OS) is available <sup>b</sup>	Sequential hormone therapy <sup>b</sup>
1.1.2	HR-positive, HER2-negative with immediately life-threatening disease or in those with rapid visceral recurrence on adjuvant hormone therapy	<i>Tamoxifen</i> Palliative <sup>a</sup> and best supportive care	Single-agent chemotherapy Combination regimens may be offered for symptomatic or immediately life-threatening disease	Single-agent chemotherapy Combination regimens may be offered for symptomatic or immediately life-threatening disease
1.1.4	HR-positive, HER2-negative Postmenopausal w/o prior adjuvant hormone therapy	<i>Tamoxifen</i>	<i>Tamoxifen</i> (nonsteroidal AI if available) Sequential hormone therapy <sup>b</sup>	A nonsteroidal AI <sup>b</sup> and a <b>CDK4/6 inhibitor</b>
1.1.5	HR-positive, HER2-negative Premenopausal	<i>Tamoxifen</i> Bilateral oophorectomy	<i>Tamoxifen</i> or alternate hormone therapy Surgical options, e.g., bilateral oophorectomy; other options: OA/OS Sequential hormone therapy if AI <sup>b</sup>	Ovarian suppression or ablation in combination with hormonal therapy (or if without exposure to prior hormone therapy, <i>tamoxifen</i> alone or ovarian suppression alone or ablation alone) Sequential hormone therapy <sup>b</sup>
1.1.6	HR-positive, HER2-negative: Postmenopausal Premenopausal with treatment-naïve	<i>Tamoxifen</i>	<i>Tamoxifen</i> or AI <sup>b</sup> Nonsteroidal if available for postmenopausal <i>Tamoxifen</i> with OA/OS if available for premenopausal or AI with OA/OS If male patients, then with a gonadotropin-releasing hormone analog	Nonsteroidal AI <sup>b</sup> and a <b>CDK4/6 inhibitor</b> combined with ovarian function suppression (if male patients, then with a gonadotropin-releasing hormone analog)
HER2-positive				
1.2.1	HER2-positive (see below for additional options for HR-positive and HER2-positive)	Palliative <sup>a</sup> and best supportive care	Chemotherapy, options include <i>anthracyclines</i> (note: doxorubicin on EML), <i>once weekly paclitaxel</i> , <i>docetaxel</i> , <i>carboplatin</i> <i>Capecitabine</i>	HER2-targeted therapy combined with chemotherapy. Options include <i>trastuzumab</i> , <b><i>pertuzumab</i></b> , and a taxane If <b><i>pertuzumab</i></b> not available, then chemotherapy and <i>trastuzumab</i> If taxane not available, then vinorelbine or platinum
1.2.2	HER2-positive, HR-positive (in special circumstances such as low disease burden, the presence of comorbidities (contradictions to HER2-targeted therapy such as congestive heart failure), and/or the presence of a long disease-free interval)	Single-agent hormone therapy ( <i>tamoxifen</i> ) Hormonal therapy with ovarian ablation.	Single-agent chemotherapy with <i>anthracyclines</i> , <i>once weekly paclitaxel</i> , <i>docetaxel</i> , <i>carboplatin</i> , <i>CMF</i> ( <i>cyclophosphamide</i> , <i>methotrexate</i> , <i>fluorouracil</i> ) Hormonal therapy alone (if AI <sup>b</sup> and <i>tamoxifen</i> available)	HER2-targeted therapy ( <i>trastuzumab</i> + <b><i>pertuzumab</i></b> ) with chemotherapy or hormonal therapy plus HER2-targeted therapy or hormonal therapy alone (latter in special circumstances) Clinicians should recommend HER2-targeted therapy-based combinations for first-line treatment, except for highly selected patients with ER-positive or progesterone receptor-positive and HER2-positive disease for whom clinicians may use endocrine therapy alone In special circumstances, such as low disease burden, the presence of comorbidities (contradictions to HER2-targeted therapy such as congestive heart failure), and/or the presence of a

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**TABLE 1. Summary of Key Guideline Recommendations (continued)**

Recommendation No.	Population	Basic	Limited	Enhanced
HER2-positive: Second-Line				
2.2.1	HER2-positive	Palliative <sup>a</sup> and best supportive care (HER2 testing likely not available)	Chemotherapy ( <i>anthracyclines, docetaxel, once weekly paclitaxel, carboplatin, CMF</i> ) <i>Capecitabine</i> <i>Capecitabine + lapatinib</i> <i>Trastuzumab</i> with second-line chemotherapy	long disease-free interval, clinicians may offer first-line endocrine therapy alone  (1) <b><i>Trastuzumab deruxtecan</i></b> If 1 not available, then 2: (2) <b><i>Trastuzumab emtansine</i></b> Other options, if 2 not available, then 3: (3) <b><i>Capecitabine + lapatinib</i></b> If 3 not available, then 4: (4) <i>Trastuzumab</i> with second-line chemotherapy
2.2.2	HER2-positive, received HER2-targeted therapy and chemotherapy in first-line	(Total mastectomy for ipsilateral in-breast recurrence if single bone metastasis only). If no medical treatment available, and no pathology, for palliative reasons, including local control, primary surgery in patients who are symptomatic when systemic anti-HER2 therapy is not available	Chemotherapy with <i>anthracyclines, docetaxel once weekly paclitaxel, and carboplatin, CMF.</i> <i>Capecitabine</i> Hormonal therapy alone	(1) <b><i>Trastuzumab deruxtecan</i></b> If 1 not available, then 2: (2) <b><i>Trastuzumab emtansine</i></b> Other options, if 2 not available, then 3: (3) <b><i>Capecitabine + lapatinib</i></b> If 3 not available, then 4: (4) <i>Trastuzumab</i> with second-line chemotherapy
2.2.3	HER2-positive If a patient finished trastuzumab-based adjuvant treatment ≤12 months before recurrence	Palliative <sup>a</sup> and best supportive care	Chemotherapy ( <i>anthracyclines, docetaxel, carboplatin, CMF, capecitabine</i> )	(1) <b><i>Trastuzumab deruxtecan</i></b> If 1 not available, then 2: (2) <b><i>Trastuzumab emtansine</i></b> Other options, if 2 not available, then 3: (3) <b><i>Capecitabine + lapatinib</i></b> If 3 not available, then 4: (4) <i>Trastuzumab</i> with second-line chemotherapy
Triple-negative: First-Line				
1.3.1	Triple-negative without known PD-L1	Palliative <sup>a</sup> and best supportive care	Single-agent chemotherapy	Single-agent chemotherapy rather than combination chemotherapy
1.3.2	Triple-negative without known PD-L1 and with symptomatic or immediately life-threatening disease	Palliative <sup>a</sup> and best supportive care	Single-agent chemotherapy Combination chemotherapy if possible	Single-agent chemotherapy Combination chemotherapy if possible
1.3.3	Triple-negative with known PD-L1 and no contraindications	Palliative <sup>a</sup> and best supportive care (PD-L1 testing not available)	Single-agent chemotherapy	Addition of immune checkpoint inhibitor to chemotherapy ( <b><i>atezolizumab</i></b> plus <b><i>nab-paclitaxel</i></b> or <b><i>pembrolizumab</i></b> plus chemotherapy) as first-line therapy
Triple-negative: Prior Treatment				
2.3.1	Triple-negative with known PD-L1 and no contraindications	Palliative <sup>a</sup> and best supportive care	Single-agent chemotherapy; start with sequencing taxane or platinum; may offer metronomic chemotherapy for disease control	Single-agent chemotherapy rather than combination chemotherapy. Start with sequencing taxane or platinum; may offer metronomic chemotherapy for disease control

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**TABLE 1.** Summary of Key Guideline Recommendations (continued)

Recommendation No.	Population	Basic	Limited	Enhanced
3.1.1	Triple-negative	Palliative <sup>a</sup> and best supportive care	Palliative <sup>a</sup> and best supportive care	Single-agent chemotherapy rather than combination chemotherapy
<i>BRCA</i> Mutations				
1.4.1.a	<i>BRCA1/2</i> mutations (HR-positive)	<i>Tamoxifen</i> —If ER-positive, then see ER-positive recommendations and/or HER2-positive, see HER2-positive recommendations Palliative <sup>a</sup> and best supportive care	<i>Tamoxifen</i> with OA AI with OA Single-agent chemotherapy rather than combination chemotherapy	<b><i>PARPi</i></b> Single-agent chemotherapy rather than combination chemotherapy
1.4.1.b	<i>BRCA1/2</i> mutations, HR-negative, HER2-negative	Palliative <sup>a</sup> and best supportive care	Single-agent chemotherapy	<b><i>PARPi</i></b> <sup>c</sup> /chemotherapy
1.4.2	HR-positive, HER2-negative, <i>BRCA1/2</i> mutations (no longer benefiting from endocrine therapy)	Palliative <sup>a</sup> and best supportive care	Single-agent chemotherapy, combination regimens may be offered for symptomatic or immediately life-threatening disease; especially <i>carboplatin</i> as first option	<b><i>PARPi</i></b> (in the first- through to third-line setting rather than chemotherapy), if not available, then Single-agent chemotherapy, combination regimens may be offered for symptomatic or immediately life-threatening disease
3.1.2	Triple-negative with germline <i>BRCA1/2</i> mutations (previously treatment with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting)	Palliative <sup>a</sup> and best supportive care	<b><i>PARPi</i></b> (for those with known mutation status)	<b><i>PARPi</i></b> (for those with known mutation status)
3.2.1	HR-positive, germline <i>BRCA1/2</i> mutation	Palliative <sup>a</sup> and best supportive care	<b><i>PARPi</i></b> (for those with known mutation status)	<b><i>PARPi</i></b> (for those with known mutation status) Single-agent chemotherapy rather than combination chemotherapy

NOTE. (1) In Basic settings, the recommendations presume that neither chemotherapy nor targeted therapy or molecular testing are available. (2) Palliative care needs should be addressed for all patients with cancer at presentation using appropriate screening, especially when disease-modifying interventions are not available. See ASCO Guideline, Osman et al<sup>2</sup> for more information. Italics = medications on Essential Medicines List (EML)<sup>3</sup> (not universally available in low-income and lower-middle-income countries [ $<50\%$ ]). Italics, bold = not on EML.

Abbreviations: AI, aromatase inhibitor; CDK, cyclin dependent kinase; CMF, cyclophosphamide, methotrexate, fluorouracil; EML, Essential Medicines List; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OA, ovarian ablation; OS, ovarian suppression; PARPi, poly(ADP-ribose) polymerase inhibitor; w/o, without.

<sup>a</sup>Palliative care may or may not include radiation therapy for symptom control.

<sup>b</sup>Patients who are premenopausal can only receive AIs if accompanied by ovarian ablation or ovarian suppression.

<sup>c</sup>Patients eligible for PARPi they previously received chemotherapy for neoadjuvant, adjuvant, or metastatic disease.

Patients with MBC for more). For patients who are postmenopausal, aromatase inhibitors (AIs) with or without CDK4/6 inhibitors can be used where available. Patients with high volume of hormone receptor–positive visceral disease where the risk of visceral crisis is a concern may be offered chemotherapy as an initial treatment.

### **QUESTION: WHAT IS THE RECOMMENDED TREATMENT FOR PATIENTS WITH HER2-POSITIVE MBC?**

Human epidermal growth factor receptor 2 (HER2)–targeted therapy is recommended for patients with HER2–positive advanced breast cancer, except for those with cardiovascular contraindications. In special circumstances, such as low disease burden, and/or the presence of a long disease free-interval, clinicians may offer first-line endocrine therapy alone.

When treating patients with HER2–positive MBC, trastuzumab, pertuzumab, and a taxane, or endocrine therapy for first-line treatment are recommended according to ASCO guidelines. However, in resource–constrained settings, the resource–stratified guideline presents a tiered list of alternatives. For example, if pertuzumab isn't available, then clinicians may offer either chemotherapy plus trastuzumab, or chemotherapy. Trastuzumab emtansine, capecitabine plus lapatinib, chemotherapy or endocrine therapy plus trastuzumab, or either without trastuzumab if the latter is not available. Navelbine can be used with trastuzumab in the frontline setting, if taxanes are not available. Another possible companion is platinum therapy.

In the second–line setting, or relapse within 12 months of adjuvant therapy, HER2–targeted therapy should be given based on prior therapy, hormone receptor status, and availability. While trastuzumab deruxtecan is the Maximal setting–recommended second–line option, in resource–constrained settings where patients and clinicians cannot access the most resource–required targeted therapy, chemotherapy or endocrine therapy may be offered with or without alternate HER2–targeted therapy regimens. The alternatives are again listed in a tiered order.

### **QUESTION: WHAT IS THE RECOMMENDED TREATMENT FOR PATIENTS WITH TRIPLE-NEGATIVE MBC?**

Patients with triple–negative, PD–L1–negative MBC should be offered single–agent chemotherapy rather than combination chemotherapy as first–line treatment in Limited as well as Enhanced settings. However, for patients with symptomatic or immediate life–threatening disease, combination therapy, if possible, may be offered.

In the second–line setting, with or without prior PD–L1 checkpoint inhibitors, clinicians may offer palliative or best supportive care in the Basic setting; chemotherapy with anthracyclines, taxanes, or carboplatin in the Limited setting and chemotherapy, if sacituzumab govitecan is unavailable,

in the Enhanced setting. In the third–line setting, for patients with triple–negative MBC, clinicians may offer chemotherapy and/or palliative care.

### **QUESTION: WHAT IS THE RECOMMENDED TREATMENT FOR PATIENTS WITH MBC AND UNKNOWN RECEPTOR STATUS?**

In Basic settings, if no immunohistochemistry testing is available, clinicians may presume hormone receptor positivity and offer tamoxifen in most cases. This is based on the higher prevalence of hormone receptor–positive tumors worldwide and the relatively low toxicity of tamoxifen. Another alternative is single–agent chemotherapy. Combination regimens may be offered for symptomatic or immediately life–threatening disease for which time may allow only one potential chance for therapy. Clinicians may offer primary surgery for palliative reasons, including local control.

### **QUESTION: WHAT IS THE RECOMMENDED TREATMENT FOR PATIENTS WITH MBC WHOSE CANCER IS PD-L1-POSITIVE OR BRCA1/2 MUTATION-POSITIVE OR HORMONE RECEPTOR-POSITIVE?**

The guideline presents treatment options for patients with MBC and positive PD–L1 or *BRCA1/2* status. For germline *BRCA1/2* mutation–positive MBC, if poly ADP–ribose polymerase inhibitor (PARPi) is unavailable, clinicians may use hormonal therapy (hormone receptor–positive MBC; with or without ovarian ablation) and chemotherapy (hormone receptor–negative MBC) in the first–line setting. In second–line setting, patients with triple–negative MBC with germline *BRCA1/2* mutations who previously received chemotherapy may be offered a PARPi rather than chemotherapy, if available. But clinicians should not offer these unless the patient has a known germline *BRCA* mutation.

This resource–stratified guideline and related ASCO guidelines present treatment for patients with these diagnoses, when quality–assured pathology results are available to guide the selection of targeted therapy, which are not yet available in many Basic and Limited Settings. The authors refer readers to the full guidelines.

### **QUESTION: WHAT IS THE RECOMMENDED TREATMENT FOR PATIENTS WITH MBC WHO ARE PREMENOPAUSAL THAT'S UNIQUE AS COMPARED TO THOSE WHO ARE POSTMENOPAUSAL?**

When treating patients who are premenopausal, the same recommendations apply as in the case of postmenopausal patients, with one caveat. Whenever hormonal therapy—besides tamoxifen—is indicated, ovarian ablation is a prerequisite. It is recommended in addition to any modality used for treatment and can be combined with either tamoxifen or an AI, depending on availability and patients' tolerance. Surgical oophorectomy or radiotherapy ablation (when

available) should be recommended rather than medical ovarian suppression strategies. For those patients who cannot tolerate ovarian ablation, tamoxifen is a reasonable alternative. Only surgeons with gynecologic surgical expertise should perform oophorectomies.

## QUESTION: WHAT IS THE ROLE OF PRIMARY TUMOR SURGERY IN MBC?

Primary tumor surgery in appropriately selected patients with de novo stage IV breast cancer controls locoregional progression, but interpretation of the limited evidence continues regarding its impact on overall survival in patients with oligometastatic or bone-only disease. Until the Expert

Panel has further prospective data, especially when medical therapy resources are constrained, surgery of the primary tumor in appropriately selected patients with limited disease burden, bone-only disease, and estrogen receptor–positive and/or HER2–positive disease, who can attain a negative margin on surgery especially those younger than 55 years, is recommended. The Panel acknowledges the controversy surrounding this recommendation and advises discussion with the patient, emphasizing the palliative benefit and the potentially positive impact. In addition, the Expert Panel suggests palliative mastectomy for patients with bleeding or progressively ulcerating tumors not responding to systemic therapy, especially in Basic or Limited settings; whenever radiation therapy is not available.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](https://www.fda.gov/oc/open-payments)).

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## APPENDIX

TABLE A1. Framework of Resource Stratification

Setting	Definition
Basic	Core resources or fundamental services that are absolutely necessary for any public health/primary health care system to function; basic-level services typically are applied in a single clinical interaction. Vaccination is feasible for highest-need populations.
Limited	Second-tier resources or services that are intended to produce major improvements in outcome such as incidence and cost-effectiveness and are attainable with limited financial means and modest infrastructure; limited-level services may involve single or multiple interactions. Universal public health interventions feasible for a greater percentage of population than the primary target group.
Enhanced	Third-tier resources or services that are optional but important; enhanced-level resources should produce further improvements in outcome and increase the number and quality of options and individual choice (perhaps ability to track patients and links to registries).
Maximal	May use high-resource settings' guidelines High-level/state-of-the-art resources or services that may be used/available in some high-resource countries and/or may be recommended by high-resource setting guidelines that do not adapt to resource constraints but that nonetheless should be considered a lower priority than those resources or services listed in the other categories on the basis of extreme cost and/or impracticality for broad use in a resource-limited environment.

NOTE. Data adapted.<sup>4-6</sup> To be useful, maximal-level resources typically depend on the existence and functionality of all lower-level resources. Maximal-level recommendations are not included in this guideline.<sup>7-12</sup>