Introduction

• This Clinical Practice Guideline (CPG) provides treatment recommendations for women with hormone receptor positive (HR+) metastatic breast cancer (MBC) who are being considered for endocrine therapy.

• Options for endocrine therapy have expanded in the last two decades, with the availability of new and effective agents.

• The forward movement of new drugs from the advanced to the early stage setting has complicated choices for metastatic disease, increasing the importance of guidelines that summarize available evidence.

• This guideline addresses endocrine therapy for the treatment of HR+ MBC. For the purposes of this guideline, postmenopausal is defined as either no menses for at least 12 months in the absence of chemotherapy, oophorectomy, or ovarian suppression with gonadotropin releasing hormone (GnRH) agonists.

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ASCO Guideline Development Methodology

The ASCO Clinical Practice Guidelines Committee guideline process includes:

• a systematic literature review by ASCO guidelines staff
• an expert panel provides critical review and evidence interpretation to inform guideline recommendations
• final guideline approval by ASCO CPGC

The full ASCO Guideline methodology supplement can be found at:
www.asco.org/guidelines/advancedendocrinebreast
Clinical Questions

CLINICAL QUESTION 1
Is there an optimal first-line endocrine therapy regimen for hormone-receptor-positive metastatic breast cancer:

1.1 For postmenopausal women: What is the optimal sequence and duration?
1.2 Should hormonal therapy be given in combination with other hormone agents or chemotherapy?
1.3 For premenopausal women: What is the optimal timing of ovarian suppression/ablation? Should all patients have their ovaries suppressed? What is the best partner hormone agent in this setting?
1.4 Are there demonstrated differences between pre- and postmenopausal patients?

CLINICAL QUESTION 2
Is there an optimal second- or later-line endocrine therapy for hormone-receptor positive metastatic breast cancer?

2.1 Should other treatment or disease-free interval play a role in treatment selection?
2.2 Which hormonal therapy should be offered?
2.3 What are the optimal timing, dose and schedule of treatment?
Clinical Questions

CLINICAL QUESTION 3
How or should endocrine therapies be used in combination/sequence with:
   3.1 mTOR inhibitors (everolimus)?
   3.2 CDK 4/6 inhibitors (palbociclib)?

CLINICAL QUESTION 4
Does estrogen/progesterone expression (high versus low expression) impact hormonal therapy considerations and modify recommendations for hormonal therapy, either the recommended agent(s) or dosing details, among pre-, peri-, and postmenopausal women?

CLINICAL QUESTION 5
How does adjuvant treatment affect recommendations for treatment in the metastatic/advanced setting?
CLINICAL QUESTION 6
In which patients or settings is hormonal therapy recommended rather than chemotherapy?
   6.1 Is there a role for combined cytotoxic and endocrine therapy?
   6.2 What is the optimal duration of treatment with hormonal therapy?

CLINICAL QUESTION 7
Is there a role for additional biomarkers in the selection of treatment for patients for HR+ disease?
   7.1 What is the role of genomic profiling/intrinsic sub-types within this population?

CLINICAL QUESTION 8
How does HER2 positivity affect treatment of patients with HR+ metastatic breast cancer?

CLINICAL QUESTION 9
What are the future directions for treatment in this patient population?
Target Population
Women with hormone receptor positive (HR+) metastatic breast cancer (MBC).

Target Audience
This Clinical Practice Guideline is targeted to both health care providers (including primary care physicians, specialists, nurses, social workers, and any other relevant member of a comprehensive multidisciplinary cancer care team) and patients.
Summary of Recommendations

Recommendation 1.1
Postmenopausal women with metastatic, HR+ positive breast cancer should be offered AIs as first-line endocrine therapy.

Recommendation 1.2
Combination hormone therapy with fulvestrant with a loading dose followed by 500 mg every 28 days combined with a nonsteroidal aromatase inhibitor may be offered for patients with metastatic breast cancer without prior exposure to adjuvant endocrine therapy.

Recommendation 1.3
Premenopausal women with metastatic hormone receptor positive breast cancer should be offered ovarian suppression/ablation in combination with hormonal therapy. Ovarian suppression with either gonadotropin releasing hormone (GnRH) agonists or ablation with oophorectomy appears to achieve similar results in metastatic breast cancer. For most patients, clinicians should use guidelines for postmenopausal women to guide the choice of hormone treatment, although sequential therapy can also be considered. Patients without exposure to prior hormone therapy can also be treated with tamoxifen or ovarian suppression/ablation alone although combination therapy is preferred. Treatment should be based on the biology of the tumor and the menopausal status of the patient with careful attention paid to production of ovarian estrogen.
Summary of Recommendations

Recommendation 1.4
Treatment should take into account the biology of the tumor and the menopausal status of the patient with careful attention paid to ovarian production of estrogen.

Recommendation 2.1
The choice of second-line hormonal therapy should take into account prior treatment exposure and response to previous endocrine therapy.

Recommendation 2.2
Sequential hormonal therapy should be offered to patients with endocrine responsive disease.

Recommendation 2.3
Fulvestrant should be administered using the 500mg dose and with a loading schedule.
Summary of Recommendations

Recommendation 3.1
Exemestane and everolimus may be offered to postmenopausal women with hormone receptor positive metastatic breast cancer progressing on prior treatment with non-steroidal AIs, either before or after treatment with fulvestrant, as PFS but not OS is improved compared to exemestane alone. This combination should not be offered as first-line therapy for patients who relapse more than 12 months from prior non-steroidal AI therapy or for those who are naïve to hormonal therapy.

Recommendation 3.2
A nonsteroidal AI and palbociclib may be offered to postmenopausal women with treatment naïve hormone receptor positive metastatic breast cancer; PFS but not OS is improved compared to the nonsteroidal AI letrozole alone. The accelerated approval of palbociclib is dependent on results of an ongoing phase III trial in the same setting.

Recommendation 4
Hormonal therapy should be offered to patients whose tumors express any level of estrogen and/or progesterone receptors

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Recommendation 5
Treatment recommendations should be offered based on the type of adjuvant treatment, disease free interval and extent of disease at the time of recurrence. A specific hormone agent may be used again if recurrence occurs > 12 months from last treatment.

Recommendation 6
Endocrine therapy should be recommended as initial treatment for patients with HR+ metastatic breast cancer except in patients with immediately life-threatening disease or in those with rapid visceral recurrence on adjuvant endocrine therapy.

Recommendation 6.1
The use of combined endocrine therapy and chemotherapy is not recommended.

Recommendation 6.2
Treatment should be given until there is unequivocal evidence of disease progression as documented by imaging, clinical examination or disease-related symptoms. Tumor markers or circulating tumor cells should not be used as the sole criteria for determining progression.
Summary of Recommendations

Recommendation 7
Use of additional biomarkers is experimental and should be reserved for selection of treatment in clinical trials. There is no routine clinical role for genomic or expression profiling in the selection of treatment for hormone receptor positive metastatic breast cancer.

Recommendation 7.1
Genomic or expression profiling should not be used to select treatment for hormone receptor positive metastatic breast cancer

Recommendation 8
The addition of HER2 targeted therapy to first-line AIs should be offered to patients with hormone receptor positive, HER2 positive metastatic breast cancer in whom chemotherapy is not immediately indicated. The addition of HER2 targeted therapy to first-line AIs improves PFS without a demonstrated improvement in OS. HER2 targeted therapy combined with chemotherapy has resulted in improvement in OS, and is the preferred first-line approach in most cases.

Recommendation 9
Patients should be encouraged to consider enrolling in clinical trials, including those receiving treatment in the first-line setting. Multiple clinical trials are ongoing or planned, with a focus on improving response to hormonal therapy in metastatic disease.
Patient and Clinician Communication

• A patient who is newly diagnosed with metastatic disease versus one for whom first- and or second- or great-line treatment has failed will likely face different issues.

• Clinical teams are encouraged to discuss the patient’s understanding of prognosis and options in creating a treatment plan, and to discuss available clinical trials at each treatment decision point.

• Teams should be prepared to present the information in this guideline in a format tailored to the patient/caregiver’s learning style, and to involve the patient as appropriate with decision making.
Health Disparities

• Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care.

• Minority racial/ethnic cancer patients suffer disproportionately from co-morbidities, they experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.

• Many other patients lack access to care because of their geography and distance from appropriate treatment facilities.

• Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

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Multiple Chronic Conditions

• Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care.

• As many patients for whom guideline recommendations apply present with MCC, any management plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision-making around guideline use and implementation.

• Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow up plan.

• This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.
## Multiple Chronic Conditions

For female patients with breast cancer that are **under 65 years** of age, the ten most common co-morbid conditions are:

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<th>Condition</th>
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<td>Hypertension</td>
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<td>Hyperlipidemia</td>
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<td>Depression</td>
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<td>Arthritis</td>
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<td>Anemia</td>
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<td>Ischemic Heart Disease</td>
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<td>Diabetes</td>
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<td>Ischemic Heart Disease</td>
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<td>COPD</td>
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<tr>
<td>Chronic Kidney Disease</td>
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<td>Heart Failure</td>
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For female breast cancer patients that are **over 65 years** of age, the ten most common co-morbid conditions are:

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<tr>
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Limitation of the Research and Future Directions

- ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

- A number of questions have not been fully explored in the current era of treatment options, such as the comparison of chemotherapy versus hormone therapy based on biologic subsets of disease, and the sequential or combination use of ovarian suppression and hormone therapy in premenopausal women.

- Ongoing trials are evaluating double antibody therapy with trastuzumab and pertuzumab in HER2 positive, ER positive disease, as well as a variety of inhibitors of CDK4/6 and PI3K.

- Future studies should strive to include at least a population of patients with multiple chronic conditions (MCC) to better represent the real world population likely to use a specific new therapy.

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Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/advancedendocrinebreast

Patient information is available at www.cancer.net
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