Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology Guideline

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ASCO SPECIAL ARTICLE

Endocrine Therapy for Hormone Receptor–Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline

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Editor's note: This American Society of Clinical Oncology clinical practice guideline provides recommendations with review and analyses of the relevant literature for each recommendation. Additional information, which may include Data Supplements, slide sets, patient versions, frequently asked questions, and clinical tools and resources, is available at www.asco.org/guidelines/advancedendocrinebreast.

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ABSTRACT

Purpose

To develop recommendations about endocrine therapy for women with hormone receptor (HR) –positive metastatic breast cancer (MBC).

Methods

The American Society of Clinical Oncology convened an Expert Panel to conduct a systematic review of evidence from 2008 through 2015 to create recommendations informed by that evidence. Outcomes of interest included sequencing of hormonal agents, hormonal agents compared with chemotherapy, targeted biologic therapy, and treatment of premenopausal women. This guideline puts forth recommendations for endocrine therapy as treatment for women with HR-positive MBC.

Recommendations

Sequential hormone therapy is the preferential treatment for most women with HR-positive MBC. Except in cases of immediately life-threatening disease, hormone therapy, alone or in combination, should be used as initial treatment. Patients whose tumors express any level of hormone receptors should be offered hormone therapy. Treatment recommendations should be based on type of adjuvant treatment, disease-free interval, and organ function. Tumor markers should not be the sole criteria for determining tumor progression; use of additional biomarkers remains experimental. Assessment of menopausal status is critical; ovarian suppression or ablation should be included in premenopausal women. For postmenopausal women, aromatase inhibitors (AIs) are the preferred first-line endocrine therapy, with or without the cyclin-dependent kinase inhibitor palbociclib. As second-line therapy, fulvestrant should be administered at 500 mg with a loading schedule and may be administered with palbociclib. The mammalian target of rapamycin inhibitor everolimus may be administered with exemestane to postmenopausal women with MBC whose disease progresses while receiving nonsteroidal AIs. Among patients with HR-positive, human epidermal growth factor receptor 2–positive MBC, human epidermal growth factor receptor 2–targeted therapy plus an AI can be effective for those who are not chemotherapy candidates.

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INTRODUCTION

This clinical practice guideline provides treatment recommendations for women with hormone receptor (HR) –positive metastatic breast cancer (MBC) who are being considered for endocrine therapy. Breast cancer is the most prevalent cancer in women in the developed world and is the second most common cause of cancer-related death for women in the United States. It was estimated that in 2015, approximately 231,840 women in the United States would be diagnosed with the disease, and almost 40,000 would die as a result of it.[1] Long-term survival outcomes are related to disease stage at presentation. Currently, a majority of patients presenting with localized disease will experience long-term disease-free survival, whereas those presenting with or who develop metastatic disease have a 5-year relative survival of only 24%,[1] and almost none are cured. HR-positive breast cancer represents the most common subset in both the early- and late-stage settings, with > 70% of tumors expressing these receptors, and recurrent disease can be observed many years after initial early-stage diagnosis.[2,3]

THE BOTTOM LINE

Endocrine Therapy for Hormone Receptor–Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline

Guideline Questions

1. Is there an optimal (defined throughout this guideline as treatments with demonstrated benefits in both treatment-related and quality-of-life outcomes) first-line endocrine therapy regimen for hormone receptor (HR) –positive metastatic breast cancer (MBC)?
    - 1.1 For postmenopausal women: What are the optimal sequence and duration?
    - 1.2 Should hormone therapy be administered in combination with other hormonal agents or chemotherapy?
    - 1.3 For premenopausal women: What is the optimal timing of ovarian suppression or ablation? Should all patients have their ovaries suppressed? What is the best partner hormonal agent in this setting?
    - 1.4 Are there demonstrated differences between pre- and postmenopausal patients?
2. Is there an optimal second- or later-line endocrine therapy for HR-positive MBC?
    - 2.1 Should other treatment or disease-free interval play a role in treatment selection?
    - 2.2 Which hormone therapy should be offered?
    - 2.3 What are the optimal timing, dose, and schedule of treatment?
3. How or should endocrine therapies be used in combination or sequence with:
    - 3.1 Mammalian target of rapamycin inhibitors (everolimus)?
    - 3.2 Cyclin-dependent kinase 4/6 inhibitors (palbociclib)?
4. Does estrogen or progesterone expression (high *v* low expression) affect hormone therapy considerations and modify recommendations for hormone therapy—either the recommended agents or dosing details—among pre-, peri-, and postmenopausal women?
5. How does adjuvant treatment affect recommendations for treatment in the metastatic or advanced setting?
6. In which patients or settings is hormone therapy recommended over chemotherapy?
    - 6.1 Is there a role for combined cytotoxic and endocrine therapies?
    - 6.2 What is the optimal duration of treatment with hormonal therapy?
7. Is there a role for additional biomarkers in the selection of treatment for patients with HR-positive disease?
    - 7.1 What is the role of genomic profiling or intrinsic subtypes in this population?
8. How does human epidermal growth factor receptor 2 (HER2) positivity affect treatment of patients with HR-positive MBC?
9. What are the future directions for treatment in this patient population?

Target Population

Women with HR-positive MBC.

Target Audience

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.

Methods

The ASCO Expert Panel was convened to conduct a systematic review of evidence from 2008 through 2015 to create recommendations informed by that evidence. Outcomes of interest included sequencing of hormonal agents, hormonal agents compared with chemotherapy, targeted biologic therapy, and treatment of premenopausal women.

ASCO Key Guideline Recommendations for HR-Positive MBC

- Hormone therapy should be offered to patients whose tumors express any level of estrogen and/or progesterone receptors.

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THE BOTTOM LINE (CONTINUED)

- Treatment recommendations should be offered on the basis of type of adjuvant treatment, disease-free interval, and extent of disease at the time of recurrence. A specific hormonal agent may be used again if recurrence occurs > 12 months from last treatment.
- Endocrine therapy should be recommended as initial treatment for patients with HR-positive MBC, except for patients with immediately life-threatening disease or for those experiencing rapid visceral recurrence during adjuvant endocrine therapy.
- Treatment should be administered until there is unequivocal evidence of disease progression as documented by imaging, clinical examination, or disease-related symptoms.
- The use of combined endocrine therapy and chemotherapy is not recommended.
- Patients should be encouraged to consider enrolling in clinical trials, including those receiving treatment in the first-line setting.

First-Line Therapy

- Postmenopausal women with HR-positive MBC should be offered aromatase inhibitors (AIs) as part of first-line endocrine therapy.
- Combination hormone therapy with a nonsteroidal AI and fulvestrant 500 mg and with a loading schedule may be offered for patients with MBC without prior exposure to adjuvant endocrine therapy.
- Premenopausal women with HR-positive MBC should be offered ovarian suppression or ablation and hormone therapy, because contemporary hormonal agents have only been studied among postmenopausal women.

Second-Line Therapy

- Sequential hormone therapy should be offered to patients with endocrine-responsive disease, except in the case of rapid progression with organ dysfunction; no specific order of agents is recommended.
- When fulvestrant is administered, it should be administered using the 500-mg dose and with a loading schedule (treatment start, day 15, day 28, then once per month).

Targeted Therapy

- A nonsteroidal AI and palbociclib may be offered to postmenopausal women with treatment-naïve HR-positive MBC, because progression-free survival (PFS) but not overall survival (OS) was improved compared with letrozole alone.
- Exemestane and everolimus may be offered to postmenopausal women with HR-positive MBC who experienced during prior treatment with nonsteroidal AIs with or without one line of prior chemotherapy, either before or after treatment with fulvestrant, because PFS but not OS was improved compared with exemestane alone.
- Fulvestrant and palbociclib may be offered to patients who experienced progression during prior treatment with AIs with or without one line of prior chemotherapy, because PFS was improved compared with fulvestrant alone. Treatment should be limited to those without prior exposure to cyclin-dependent kinase 4/6 inhibitors.
- The addition of HER2-targeted therapy to first-line AIs should be offered to patients with HR-positive, HER2-positive MBC in whom chemotherapy is not immediately indicated.
- Genomic or expression profiling should not be used at this time to select treatment for HR-positive MBC.

Qualifying Statements

- Tumor markers or circulating tumor cells should not be used as the sole criteria for determining disease progression.
- Providers should recognize and acknowledge special issues faced by premenopausal women with MBC, including loss of fertility.
- 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.
- There is more toxicity associated with the combination of exemestane and everolimus compared with other single-agent endocrine options.
- There is more toxicity associated with the combination of palbociclib and endocrine therapy compared with other single-agent endocrine options.

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THE BOTTOM LINE (CONTINUED)

- Palbociclib should be administered once per day for 21 days every 28 days; the primary toxicity is neutropenia. Blood counts should be monitored every 14 days for the first two 28-day cycles, then at the start of each subsequent cycle, with neutropenia managed by dose delays and reductions. Although no data exist at present, any AI could be substituted depending on individual tolerance. On the basis of the data from PALOMA-3, palbociclib can also be combined with fulvestrant in the second-line setting or greater, including after one line of chemotherapy.
- Chemotherapy in combination with HER2-targeted therapy is indicated in de novo and visceral dominant disease, because this treatment offers a survival benefit compared with chemotherapy alone.
- There is no routine clinical role for genomic or expression profiling in the selection of treatment for HR-positive MBC.

Additional Resources

More information, including Data Supplements with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at http://www.asco.org/guidelines/advancedendocrinebreast and http://www.asco.org/guidelineswiki. Patient information is available at http://www.cancer.net/.

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.

Options for endocrine therapy have expanded in the last two decades, with the availability of new and effective agents. Many of these treatments have now been incorporated into the early-stage setting, with both extended duration and use of sequential therapy. 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. In addition, a greater understanding of the biologic pathways that contribute to hormone resistance has led to approval of targeted agents administered in combination with hormone therapy, including trastuzumab, everolimus, and palbociclib, and multiple studies are ongoing.[4-7] Treatment of premenopausal women is a particular challenge, with questions regarding timing of ovarian suppression and optimal use of hormonal agents. This guideline will address endocrine therapy for the treatment of HR-positive 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.

INITIAL TREATMENT: ENDOCRINE THERAPY OR CHEMOTHERAPY

One important question is whether first-line therapy for HR-positive MBC should be chemotherapy or endocrine therapy. There are limited data to answer this question amid current treatment options. Historical literature suggests that neither survival nor quality of life (QoL) is improved by treating patients with chemotherapy when hormone therapy has a reasonable chance of providing disease control.[8] Randomized trials conducted in previous decades for patients with de novo metastatic disease suggested equivalent long-term rates of tumor control and survival with either approach. In addition, an analysis of hormone therapy trials in the first-line setting demonstrated similar duration of disease control regardless of visceral organ involvement in the absence of immediately life-threatening disease.[9]

A second question is whether there is benefit in combining chemotherapy and hormone therapy. Again, historical data suggest that sequential single-modality treatment is equivalent or preferred to combination therapy, although formal comparisons are weak with respect to clinically important end points including symptom control, progression-free survival (PFS), and overall survival (OS).[10,11] For these reasons, the recommended initial course of treatment for HR-positive MBC is endocrine therapy. The Expert Panel acknowledges that there are situations in which chemotherapy is appropriate as initial therapy for HR-positive MBC, including in patients with immediately life-threatening disease, where the time to treatment response may be critical and where there may be a near-term advantage in chemotherapy. Chemotherapy-appropriate situations may also include those where tumor biology (eg, extremely low levels of estrogen receptor [ER]) makes endocrine treatment less likely to be effective or in patients with HR-positive, human epidermal growth factor receptor 2 (HER2) –positive breast cancer, for whom combining chemotherapy and anti-HER2 treatments has a survival advantage. Fortunately, rapidly progressive immediately life-threatening disease is relatively uncommon among women with HR-positive MBC. For ASCO guidance on the use of chemotherapy in advanced breast cancer, please see the Clinical Practice Guideline on chemotherapy and targeted therapy for women with HER2-negative (or unknown) advanced breast cancer.[11a]

COMBINATIONS OF HORMONE THERAPY OR HORMONE THERAPY WITH TARGETED AGENTS

Existing data suggest that combinations of hormone therapy should be considered only in specific situations, although ongoing

trials are evaluating additional settings and drug doses. Discordant results have been reported on combinations of the selective ER downregulator fulvestrant and aromatase inhibitors (AIs) in the first-line setting; one randomized study showed improved PFS and OS, favoring the combination over the AI alone, but another with a similar design showed equivalent PFS and OS.[12,13] Subset analysis suggested that the survival benefit was primarily observed in patients without exposure to prior endocrine therapy. A phase II trial comparing fulvestrant with anastrozole as first-line therapy for hormone-naïve MBC demonstrated no improvement in the primary end point of clinical benefit, but subsequent follow-up suggested improved time to progression (TTP) and OS with use of fulvestrant; an ongoing phase III trial is exploring this comparison (Data Supplement 8 provides details on the FALCON [A Global Study to Compare the Effects of Fulvestrant and Arimidex in a Subset of Patients With Breast Cancer] trial [ClinicalTrials.gov identifier NCT01602380]).[14,15] Few studies have demonstrated a survival benefit for one treatment compared with another in postmenopausal patients with HR-positive MBC; for that reason, variation in sequencing or the use of combination therapy can be offered. Hormone therapy administered in combination with agents targeted to pathways implicated in hormone resistance is under intense evaluation, with both failures and recent successes. The mammalian target of rapamycin (mTOR) inhibitor everolimus, administered in combination with the steroidal AI exemestane in patients with progressive disease or disease resistant to nonsteroidal AIs (letrozole or anastrozole), demonstrated improved PFS compared with exemestane alone but was associated with increased toxicity and did not improve OS; these data led to US Food and Drug Administration (FDA) approval of everolimus and exemestane.[4,16] The addition of the cyclin-dependent kinase (CDK) 4/6 inhibitor palbociclib, administered as first-line therapy in combination with the nonsteroidal AI letrozole, in an open-label phase II trial also significantly improved PFS without improving OS.[7] This combination was well tolerated, although the study was small. Accelerated approval for palbociclib was granted early in 2015, pending results from a phase III trial with a similar design (Data Supplement 8 provides details on the PALOMA-2 [Palbociclib: Ongoing Trials in the Management of Breast Cancer] trial). Palbociclib was also studied as second-line therapy for HR-positive MBC in combination with fulvestrant in a placebo-controlled phase III trial. The addition of palbociclib significantly improved PFS, with a toxicity profile similar to that shown in the phase II trial; survival data are immature.[17] Global QoL was generally maintained in the palbociclib arm, but it deteriorated in those receiving placebo. Therapy targeted to HER2 combined with hormonal agents in patients with HR-positive, HER2-positive MBC also resulted in improved PFS compared with hormonal agents alone, without improved survival.[5,6] Controversy exists about how to use these novel drugs in clinical practice. Additional agents targeting a number of pathways are in phase III trials as well (Data Supplement 8).

TREATMENT OF PREMENOPAUSAL WOMEN

Premenopausal women have generally not been included in clinical trials testing hormone therapy, particularly in the first-line setting. As in postmenopausal women, the choice of treatment in the metastatic setting is dependent on treatment administered for early-stage disease. Questions are ongoing regarding the use of ovarian suppression in combination or in sequence with hormonal agents[18,19] and the sequencing of tamoxifen and AIs. Randomized trials have shown a survival advantage with the combination of ovarian suppression and hormone therapy, and all contemporary hormonal agents have been studied only in postmenopausal women.[14,15,20-26] Data from the early-stage setting may offer additional insight.

BIOPSIES FOR METASTATIC DISEASE

The panel considers it mandatory for all patients to have ER and HER2 status determined in their cancers. Often a biopsy is recommended to determine or confirm whether a suspicious lesion represents MBC; in this case, markers should be obtained.[27] In addition, the panel believes that in most settings, recurrent disease should be biopsied whenever feasible for determination of tumor ER and HER2 status, because these markers guide therapy for metastatic disease. A number of studies have reported discordance between marker status in early- and late-stage disease, which results in a change in management in up to 14% of patients.[28] However, at present, there is a lack of clear evidence that a change in markers in the metastatic lesion is predictive of response to therapy.

Caution should be exercised in interpreting information obtained from bone biopsies, because processing may alter ER and/or HER2 testing results, or biopsies may contain few tumor cells, and results may not be reliable.[29] Although biopsies are recommended in the majority of patients to confirm diagnosis and evaluate markers, there may be some patients for whom there is adequate information available from the primary tumor. Given the increasing number of options for the treatment of patients with MBC with hormone therapy and the controversies outlined, a clinical practice guideline is warranted.

CLINICAL PRACTICE GUIDELINES

Practice guidelines are systematically developed statements that assist practitioners and patients in making decisions about care. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, flexibility, clarity, a multidisciplinary process, review of evidence, and documentation. Guidelines may be useful in producing better care and decreasing cost. Specifically, use of clinical guidelines may provide improvements in outcomes, improvements in medical practice, a means for minimizing inappropriate practice variation, decision support tools for practitioners, points of reference for medical orientation and education, criteria for self-evaluation, indicators and criteria for external quality review, assistance with reimbursement and coverage decisions, criteria for use in credentialing decisions, and identification of areas where future research is needed.

Panel Composition

To address the clinical question, an Expert Panel was convened with multidisciplinary representation in medical oncology, radiation oncology, psycho-oncology, patient advocacy, and guideline methodology. The Expert Panel was led by two co-chairs who had the primary responsibility for the development and timely completion of the guideline. The Expert Panel members are listed in Data Supplement 6.

Guideline Development Process

The Expert Panel members, who met face to face and via teleconference and corresponded through e-mail, were asked to contribute to the development of the guideline, provide critical review, interpret evidence, and finalize the guideline recommendations based on consideration of the evidence. Members of the Expert Panel were responsible for drafting the penultimate version of the guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and publication. All ASCO guidelines are reviewed and approved by the ASCO Clinical Practice Guideline Committee before publication.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria; consulting or advisory role; speakers bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the panel did not disclose any relationships constituting a conflict under the Policy.

METHODS

Systematic Literature Review

ASCO guidelines are based on systematic reviews. A protocol for each guideline defines the parameters for a targeted literature search, including relevant study designs, literature sources, types of reports, and prespecified study selection criteria for literature identified.

Literature Search Strategy

The MEDLINE (OVID: 2008 through week 4 of April 2014) and Cochrane Library databases (http://www.cochranelibrary.com; to Issue 3 of March 2013) were searched for evidence reporting on outcomes of interest. Additionally, the San Antonio Breast Cancer Symposium (2011 to 2014) and ASCO abstracts (2012 to 2014) were searched for reports on systematic reviews (with or without meta-analyses) and randomized controlled trials (phase II or III) using the keywords "advanced" and "metastatic" and were reviewed for terms relating to HR status, publication type, and study design. Reference lists from seminal papers and recent review articles were scanned for additional citations, and known updates of included evidence were obtained as available. A targeted literature search update was performed in June 2015 to obtain the most recent evidence. The literature search strategy used in the MEDLINE database is available in Data Supplement 1.

Study Selection Criteria

Articles were selected for inclusion in the systematic review of the evidence if they were fully published or abstract reports of systematic reviews (with or without meta-analyses) or randomized controlled trials (phase II or III), published in English, that reported on any of the following interventions: endocrine therapies, including selective ER modulators (tamoxifen or toremifene), ER downregulators (fulvestrant), progestins (megestrol acetate or medroxyprogesterone), luteinizing hormone–releasing hormone analogs (goserelin, leuprorelin, or buserelin), nonsteroidal third-generation AIs (anastrozole or letrozole), and steroidal third-generation AIs (exemestane); mTOR inhibitors (everolimus or temsirolimus); CDK 4/6 inhibitors (palbociclib); estrogens; and chemotherapy.

Selected articles made any of the following comparisons: single-agent versus single-agent hormone therapies, single-agent versus combination endocrine therapies, endocrine therapy with or without HER2-targeted therapies, endocrine therapy with or without mTOR inhibitors, endocrine therapy with or without CDK 4/6 inhibitors, and endocrine therapy with or without novel agents. Articles were also required to report on primary outcomes of interest (including OS, PFS or TTP, or clinical benefit rate [CBR; stable disease plus response rate]) or secondary outcomes of interest (including time to initiation of chemotherapy, toxicity, or QoL as measured by a validated, reliable instrument [eg, Short Form Health Survey 36]). Articles were excluded from the systematic review if they were noncomparative studies.

Data Extraction

Literature search results were reviewed and deemed appropriate for full-text review by an ASCO staff member in consultation with the panel co-chairs. Data were extracted by one ASCO staff member and subsequently checked for accuracy through an audit of the data by another ASCO staff member. Disagreements were resolved through discussion and consultation with the co-chairs if necessary.

Revision Dates

The co-chairs determine the need for guideline updates or revisions on the basis of periodic review and consideration of the literature. If new and compelling data are identified, the Expert Panel or an update committee is reconvened to discuss revisions to the document.

RESULTS

A total of 36 articles, including seven systematic reviews with meta-analyses[8,30-35] (Table 1) and 29 individual trial reports,[6,7,12,13,15,17,20,22-26,36-52] met the inclusion criteria. Four of these trials[15,21,42,50] had their findings published in multiple reports,[4,5,14,21,50] which are indicated in the tables and text where appropriate. The 29 primary studies[6,7,12,13,15,17,20,22-26,36-52] included nine trials[15,20,22-26,36,37] that compared single-agent versus single-agent hormone therapies, three[12,13,38] compared single-agent versus combination endocrine therapies, one[39] compared endocrine therapy with or without epidermal growth factor receptor (EGFR) –targeted therapies, four[6,40-42] compared endocrine therapy with or without HER2-targeted therapies, three[43-45] compared endocrine therapy with or without mTOR inhibitors, and two compared endocrine therapy with or without CDK 4/6 inhibition[7,17] and, for novel agents; one trial[46] compared endocrine therapy with or without rearranged during transfection (RET) vascular endothelial growth factor receptors (VEGFRs) and an EGFR tyrosine kinase inhibitor (TKI); one[47] compared endocrine therapy with or without an insulin-like growth factor receptor (IGFR) antibody; two[48,49] compared endocrine therapy with or without a VEGF antibody, one[50] compared endocrine therapy with or without a histone deacetylase (HDAC) inhibitor, and two[51,52] compared endocrine therapy with a pan–phosphatidylinositol 3-kinase (PI3K) inhibitor. All trial data are listed in Tables 2–5, and descriptions of the regimens used in each trial are provided in Data Supplement 7. The outcomes for each comparison will be discussed in their own section.

Systematic Reviews With or Without Meta-Analyses

A total of seven systematic reviews with meta-analyses were obtained.[8,30-35] One[8] compared single-agent endocrine therapy against single-agent chemotherapy, three compared single-agent versus single-agent hormone therapies,[30-32] two compared single-agent versus combination endocrine therapies,[33,34] and one compared endocrine therapy with or without mTOR inhibitors.[35]

Five of these systematic reviews detected significant differences between treatments. Wilcken et al,[8] in a comparison of single-agent endocrine therapy against single-agent chemotherapy, found a significant benefit in response rates associated with chemotherapy. Chi et al,[30] in a comparison between toremifene and tamoxifen, detected no differences between the two in efficacy, although toremifene was associated with significantly greater vaginal bleeding and lower serum triglycerides. Cope et al,[31] in a comparison among fulvestrant at two different doses, anastrozole, megestrol, exemestane, and letrozole at two doses found fulvestrant at 500 mg superior to fulvestrant at 250 mg, megestrol, and anastrozole for PFS. Xu et al,[32] comparing AIs with tamoxifen, found AIs superior for both response and CBR. Finally, Bachelot et al,[35] in a comparison between exemestane plus the mTOR inhibitor everolimus with everolimus plus tamoxifen or fulvestrant, found exemestane plus everolimus superior to fulvestrant 250 mg and fulvestrant 500 mg for both PFS and TTP. Details are listed in Table 1.

Study Characteristics

Single-agent versus single-agent hormone therapies. A total of nine trials[15,20-26,37] were obtained that compared single-agent versus alternate single-agent hormone therapies. Four[15,22,23,37] of these reported on first-line treatment, and five[20,21,24-26] reported on second-line treatment. These nine trials included a total of 3,661 patients, ranging from a low of 103[23] to a high of 736.[36] Median age ranged from a low of 53.4 years[26] to a high of 72.6 years.[23] All nine trials reported that only postmenopausal patients were included, and three[20,22,37] reported that HR-negative patients were included, although the number of HR-positive patients were the majority (94.8%,[22] 94.2%,[37] and 98.3%,[20] respectively). In the three trials[22,24,25] that reported on HER2 status, a majority of patients were HER2-negative. Seven trials[20,22-26,37] reported on patients who had received previous chemotherapy, and four[20,21,24,37] reported on patients who had received previous endocrine therapy. Details are listed in Table 2.

Single-agent versus combination endocrine therapies. Three trials[12,13,38] were obtained that compared single-agent versus combination endocrine therapies; two[12,13] of these were in the first-line setting. These three trials included a total of 1,931 patients, ranging from a low of 514[13] to a high of 723.[38] The median age ranged from a low of 63 years[13] to a high of 66 years.[38] Two trials[12,38] reported 100% of patients being postmenopausal, whereas the third trial did not report menopausal status. Although the number of HR-positive patients included in these trials approached 100%, two[13,38] reported including small numbers of HR-negative patients (0.9%[38] and 2.3%[13]). Two[12,38] of the trials reported on HER2 status, with Johnston et al[38] reporting 93% of patients being HER2 negative or unknown and Mehta et al[12] reporting approximately 90% of patients being HER2 negative. Both Mehta et al[12] and Bergh et al[13] reported the number of patients who had received prior adjuvant chemotherapy and/or endocrine therapy. Details are listed in Table 2.

Endocrine therapy with or without HER2-targeted therapies. Four trials[6,40-42] were found that compared endocrine therapy with or without HER2-targeted therapies, all in the first-line setting. These four trials included a total of 1,133 patients, ranging from a low of 57[41] to a high of 359.[5] The median age ranged from a low of 54 years[6] to a high of 61.5 years.[41] All of these trials included only postmenopausal patients. Although the proportion of HR-positive patients included in these five trials approached 100%, three trials reported including small numbers of HR-negative patients.[40-42] Two trials[5,6] did not report on HER2 status. Three trials[6,40,42] reported patients who had received prior chemotherapy, and four[6,40-42]

Table 1. Main Findings From Systematic Review (all included meta-analyses)

Study	Evidence Base	Main Findings
Endocrine *v* chemotherapy		
Wilcken[8]	Six trials including 692 patients with MBC (for OS comparison)	No significant difference in OS was detected (hazard ratio, 0.94; 95% CI, 0.79 to 1.12; $P = .5$), with nonsignificant heterogeneity detected
	Compared single-agent endocrine treatment with single-agent chemotherapy	Significant benefit in response rates (eight trials involving 817 women) for chemotherapy over endocrine therapy was detected (RR, 1.25; 95% CI, 1.01 to 1.54; ***P* = .04**)
		Authors conclude that standard first-line treatment for patients with MBC should be endocrine therapy rather than chemotherapy, except in presence of rapidly progressing disease
Single-agent *v* single-agent hormone therapies		
Chi[30]	23 trials including 7,242 patients (patients with advanced breast cancer were subset of total population)	Toremifene was associated with more vaginal bleeding (OR, 0.45; 95% CI, 0.26 to 0.80; ***P* < .05**) and greater decrease in serum triglyceride levels (SMD, −1.15; 95% CI, −1.90 to −0.39; ***P* < .05**) than tamoxifen
	Compared toremifene and tamoxifen	Evidence suggests toremifene could be an alternative to tamoxifen for patients with advanced breast cancer
Cope[31]	11 RCTs including 5,808 postmenopausal women with advanced breast cancer after endocrine therapy failure	Fulvestrant 500 mg was superior to fulvestrant 250 mg, megestrolacetate, and anastrozole for PFS (***P* < .05**)
	Compared fulvestrant 500 mg, fulvestrant 250 mg, fulvestrant 250 mg loading dose, anastrozole 1 mg, megestrol acetate, letrozole 2.5 mg, letrozole 0.5 mg, and exemestane	
Xu[32]	Six RCTs including 2,560 postmenopausal patients with HR-positive advanced breast cancer	AIs were superior to tamoxifen alone for response (ORR; OR, 1.56; 95% CI, 1.17 to 2.07; ***P* < .05**) and CBR (OR, 1.70; 95% CI, 1.24 to 2.33; ***P* < .05**)
	Compared AIs *v* tamoxifen	
Single-agent *v* combination endocrine therapies		
Tan[33]	Two RCTs including patients with HR-positive advanced breast cancer (total patients, NR)	None of the comparisons for PFS, OS, or response showed statistically significant difference
	Compared fulvestrant + AI *v* AI alone (both studied anastrozole in combination with fulvestrant)	
Valachis[34]	Four RCTs including 2,125 patients with HR-positive advanced breast cancer	No difference detected between fulvestrant + AIs and tamoxifen for OS, TTP, CBR, or ORR
	Compared fulvestrant + AIs *v* tamoxifen	Hormonal agents other than fulvestrant were associated with great likelihood of joint disorders (***P* < .05**)
Endocrine therapy ± mTOR inhibitors		
Bachelot[35]	Six RCTs (total patients, NR)	Everolimus + exemestane was superior to fulvestrant 250 mg and fulvestrant 500 mg for PFS and TTP (hazard ratio, 0.47; 95% CI, 0.38 to 0.58; ***P* < .05** and hazard ratio, 0.59; 95% CI, 0.45 to 0.77; ***P* < .05**, respectively)
	All patients had HR-positive, HER2-negative advanced breast cancer	Analysis suggests that everolimus + exemestane is superior to fulvestrant 250 mg and 500 mg for PFS and TTP in patients with HR-positive, HER2-negative breast cancer with disease progression after endocrine therapy; however, there are no RCTs currently available providing direct comparison
	Included studies identified by systematic literature review (sources: Cochrane Library, National Horizon Scanning Centre, and NICE Web sites)	
	Comparisons were: everolimus + exemestane or everolimus + tamoxifen *v* fulvestrant	

Abbreviations: AI, aromatase inhibitor; CBR, clinical benefit rate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; NICE, National Institute for Health and Care Excellence; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RR, response rate; TTP, time to progression.

included patients who had received prior endocrine therapy. Details are listed in Table 2.

Endocrine therapy with or without mTOR inhibitors. Three trials[43,44,50] were found that compared endocrine therapy with or without mTOR inhibitors, two[43,44] in first-line treatment and one[45] in the second-line setting. These three trials included a total of 1,945 patients, ranging from a low of 111[43] to a high of 1,110.[44] The median age ranged from a low of 61 years[45] to a high of 66 years.[43] All of the patients included in these three trials were postmenopausal and HR-positive, except those in the trial reported by Wolff et al,[44] which included a small number of HR-negative patients. The trial by Piccart et al[4,45,50] included 100% HER2-negative patients, and the trial by Bachelot et al[43] included 93% (tamoxifen arm) and 98% (tamoxifen plus everolimus arm) HER2-negative patients. One trial[44] included > 50% HER2-positive patients. Two[43,44] included patients who had received previous chemotherapy. All three trials included patients that had received prior endocrine therapy. Details are listed in Table 2.

Endocrine therapy with or without a CDK 4/6 TKI. Two trials[7,17] were found comparing endocrine therapy with or without

a CDK 4/6 TKI. One phase II trial[7] in the first-line setting included 165 postmenopausal patients, and the second phase III trial[17] in the second-line or greater setting included 521 postmenopausal patients, all with HR-positive disease. Details are listed in Table 2.

Endocrine Therapy With or Without Novel Agents

Endocrine therapy with or without an RET, VEGFR, and EGFR TKI. One phase II trial[46] in the first-line setting was found that compared endocrine therapy with or without a RET, VEGFR, and EGFR TKI. This trial included 129 patients with a median age of 59 years. Some patients had received previous chemotherapy (18%) or endocrine therapy (73%). Details are listed in Table 2.

Endocrine therapy with or without an IGFR antibody. One phase II trial[47] in the second-line setting was obtained that compared endocrine therapy with or without an IGFR antibody. This trial included 156 patients with a median age of 61.5 years. This trial included a small number of HR-negative patients, and a majority were HER2 negative as well. Some patients had received previous chemotherapy (endocrine therapy arm, 64%; endocrine therapy plus IGFR arm, 67%) or endocrine therapy (100%). Details are listed in Table 2.

Endocrine therapy with or without a VEGF antibody. Two phase III trials[48,49] in the first-line setting were found that compared endocrine therapy with or without a VEGF antibody. One trial included 334 patients, and the second trial included 343 patients. All included patients were postmenopausal, and a majority or all had HR-positive disease. Details are provided in Table 2.

Endocrine therapy with or without an HDAC TKI. One phase II trial[50] in the second-line setting was found comparing endocrine therapy with or without an HDAC TKI. This trial included 130 patients with a median age of 62.5 years. All included patients were postmenopausal, with only a small number of HR-negative patients included. Some patients had received previous chemotherapy (endocrine therapy arm, 42%; endocrine therapy plus HDAC TKI arm, 34%) or endocrine therapy (endocrine therapy arm, 86%; endocrine therapy plus HDAC TKI arm, 84%). Details are listed in Table 2.

Endocrine therapy plus a pan-PI3K inhibitor. Two trials[51,52]—one phase II[51] and one phase III,[52] both conducted in the second-line setting—were found comparing endocrine therapy plus either a pan-PI3K inhibitor or placebo. These two trials included a total of 1,147 patients, ranging from a low of 168[51] to a high of 1,147.[52] Median age was 61 years in both trials. All patients included in the trials were postmenopausal, all were HR positive, approximately 25% of all patients in both trials had received prior chemotherapy for MBC, and all patients had received prior endocrine therapy. Details are listed in Table 2.

Study Quality

As seen in the Study Quality Assessment Table in the Methodology Supplement (online only), study quality was formally assessed for the 29 trials identified. Design aspects related to individual study quality were assessed by one reviewer and independently audited by another, with factors such as blinding, allocation concealment (blinding to treatment arm), placebo control, intention to treat, funding sources, and so on considered. The overall risk of bias was assessed as either low to intermediate or intermediate for the included trials. Refer to the Methodology Supplement for definitions of ratings for overall potential risk of bias.

Outcomes

Data on key outcomes of interest are listed in Table 3, separated according to the comparison being made. Because all outcomes are summarized in detail in Table 3, only trials that detected a significant difference for any of the outcomes of interest will be described here, separated by comparison.

Single-agent versus single-agent hormone therapies. In a phase II first-line trial in which 205 patients were randomly assigned to fulvestrant or anastrozole, Robertson et al[15] detected a TTP benefit (23.4 *v* 13.1 months; $P < .05$) in favor of fulvestrant. The primary outcome of this trial was CBR, which was similar between the two arms (72.5% *v* 67%; $P = .386$). OS was not defined as an end point in the original protocol, but it was assessed by a protocol amendment; 17% of patients were lost to follow-up. Median OS was 54.1 versus 48.4 months ($P = .041$) in this exploratory analysis. In a phase III second-line trial in which 736 patients were randomly assigned to fulvestrant 250 mg or fulvestrant 500 mg, Di Leo et al[21] detected benefits in OS (26.4 *v* 22.3 months; $P < .05$) and PFS (6.5 *v* 5.5 months; $P < .05$) in favor of the higher-dose treatment.

Single-agent versus combination endocrine therapies. In a phase III first-line trial in which 694 patients were randomly assigned to anastrozole alone or the combination of fulvestrant 250 mg plus anastrozole, Mehta et al[12] reported improved PFS (15 *v* 13.5 months; $P < .05$) and OS (47.7 *v* 41.3 months; $P < .05$) in favor of the combination treatment. In a second phase III first-line trial, 514 patients were randomly assigned to anastrozole alone or the combination of fulvestrant 250 mg plus anastrole. Bergh et al[13] reported no difference in either TTP (10.2 *v* 10.8 months; $P = .91$) or OS (38.2 *v* 37.8 months; $P = 1.00$). There were demographic differences between the patients enrolled in the two trials, suggesting that the benefit from combination therapy might have occurred primarily in patients with de novo, untreated metastatic disease.

Endocrine therapy with or without HER2-targeted therapies. In a phase III first-line trial in which 219 patients were randomly assigned to letrozole alone or letrozole with lapatinib, Schwartzberg et al[42] detected benefits in PFS (8.2 *v* 3 months; $P < .05$) and CBR (48% *v* 29%; $P < .05$) in favor of the combination treatment. In another phase III first-line trial in which 207 patients were randomly assigned to anastrozole alone or anastrozole with trastuzumab, Kaufman et al[6] detected benefits in PFS (4.8 *v* 2.4 months; $P < .05$) and CBR (42.7% *v* 27.9%; $P < .05$) in favor of the combination treatment. Finally, in a third phase III trial in which 295 patients previously treated with an AI were randomly assigned to fulvestrant with or without lapatinib regardless of HER2 status, Burstein et al[40] reported no benefit in either PFS or OS. In the HER2-positive subset (54 patients [18%]), a nonsignificant improvement in PFS (5.9 *v* 3.3 months; $P = .53$) was observed.

Endocrine therapy with or without mTOR inhibitors. In a phase II open-label trial in which 111 patients previously treated with letrozole or anastrozole were randomly assigned to tamoxifen or tamoxifen with everolimus, Bachelot et al[43] detected benefits in CBR (61% *v* 42%; $P < .05$) in favor of tamoxifen with everolimus. An exploratory analysis suggested benefit in both OS (32.9 *v* median not yet reached; $P < .05$) and TTP (8.6 *v* 4.5 months; $P < .05$) with the addition of everolimus to tamoxifen. In an update of a phase III second-line trial in which 724 patients were randomly

Table 2. Study Characteristics

Source	Treatment Arm	Treatment Line	No. of Patients	Patient Characteristics: Median (range) Age (years)	Patient Characteristics: Menopausal Status (%) Pre	Patient Characteristics: Menopausal Status (%) Post	Disease Characteristics (%): HR Positive	Disease Characteristics (%): HER2 Negative	Previous Therapy (%): Chemotherapy	Previous Therapy (%): Endocrine
Single-agent *v* single-agent hormone therapies										
Phase II										
Llombart-Cussac[23]; 2001-2003; SBCG 2001/03	Exemestane	First	51	67.9 (45-94)	0	100	100	NR	47	NR
	Anastrozole		52	72.6 (46-85)	0	100	100	NR	50	NR
Robertson[14,15]; FIRST	Fulvestrant	First	102	NR	0	100	100	NR	28.4 (adjuvant)	27.5 (adjuvant)
	Anastrozole		103	NR	0	100	100	NR	24.3 (adjuvant)	22.3 (adjuvant)
Ohno[24]; FINDER-1	Fulvestrant (250 mg per month)	Second	45	61 (50-77)	0	100	100	80	55.6	100
	Fulvestrant (250 + 500 mg on day 0, 250 mg on days 14 and 28, and monthly thereafter)		51	62 (43-86)	0	100	100	90.8	72.5	100
	Fulvestrant (500 mg per month + 500 mg on day 14 of month 1)		47	61 (45-83)	0	100	100	85.1	70.2	100
Pritchard[25]; FINDER-2	Fulvestrant (250 mg per month)	Second	47	63 (42-88)	0	100	100	78.7	59.6	100
	Fulvestrant (250 + 500 mg on day 0, 250 mg on days 14 and 28, and monthly thereafter)		50	69 (38-85)	0	100	100	72.5	49	100
	Fulvestrant (500 mg per month + 500 mg on day 14 of month 1)		46	67 (49-85)	0	100	100	69.6	56.5	100
Phase III										
Di Leo[21,36]; CONFIRM	Fulvestrant 250 mg	Second	374	61	0	100	100	NR	NR	100
	Fulvestrant 500 mg		362	61	0	100	100	NR	NR	100
Iwata[22]; 2005-2010	Exemestane	First	149	63.4 (54.1-72.7)	0	100	94.8	93.9	69.1	NR
	Anastrozole		149	64 (55-73)	0	100	98.2	93.6	67.1	NR
Xu[26]; 2005-2007	Fulvestrant	Second	121	53.4 (33-78)	0	100	100	NR	100	100
	Anastrozole		113	54.8 (31-77)	0	100	100	NR	100	100
Chia[20]; 2003-2005; EFECT	Fulvestrant	Second	351	63 (38-88)	0	100	98.3	NR	24.8	89.2
	Exemestane		342	63 (32-91)	0	100	98.2	NR	21.6	86
Paridaens[37]; 1996-2002	Exemestane	First	182	63 (37-86)	0	100	96.2	NR	30.2	11.5
	Tamoxifen		189	62 (37-87)	0	100	94.2	NR	33.3	8.5

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Table 2. Study Characteristics (continued)

Source	Treatment Arm	Treatment Line	No. of Patients	Patient Characteristics: Median (range) Age (years)	Patient Characteristics: Menopausal Status (%) Pre	Patient Characteristics: Menopausal Status (%) Post	Disease Characteristics (%): HR Positive	Disease Characteristics (%): HER2 Negative	Previous Therapy (%): Chemotherapy	Previous Therapy (%): Endocrine
Single-agent *v* combination endocrine therapies										
Phase II										
Johnston[38]; 2004-2010; SoFEA	Fulvestrant + placebo	Second	231	63.4 (57-73.5)	0	100	99.1	61 (HER2 negative or unknown, 94)	NR	100
	Fulvestrant + anastrozole		243	63.8 (57-72)	0	100	100	50 (HER2 negative or unknown, 93)	NR	100
	Exemestane		249	66 (59.2-75)	0	100	99.6	57 (HER2 negative or unknown, 93)	NR	100
Phase III										
Bergh[13]; 2004-2008; FACT	Anastrozole alone	First	256	63 (36-90)	NR	NR	97.7	NR	49.6 (adjuvant)	65.6
	Fulvestrant + anastrozole		258	65 (33-86)	NR	NR	98.4	NR	41.9 (adjuvant)	69.8
Mehta[12]; 2004-2009; SWOG 0226	Anastrozole alone → fulvestrant	First	345	65 (36-91)	0	100	100	91.5	29.9 (adjuvant)	40 (adjuvant)
	Anastrozole + fulvestrant		349	65 (27-92)	0	100	100	89.6	37 (adjuvant)	40 (adjuvant)
Endocrine therapy ± EGFR-targeted therapies										
Phase II										
Johnston[39]; 2010-2012; MINT	Placebo	First	121	NR	0	100	NR	NR	NR	NR
	Anastrozole + AZD8931* 20 mg		118	NR	0	100	NR	NR	NR	NR
	Anastrozole + AZD8931 40 mg		120	NR	0	100	NR	NR	NR	NR
Endocrine therapy ± HER2-targeted therapies										
Phase III										
Burstein[40]; CALGB 40302	Fulvestrant + placebo	First	145	NR	0	100	97	78	17	97
	Fulvestrant + lapatinib		146	NR	0	100	99	84	16	97
Huober[41]; 2003-2007; ELECTRA	Letrozole alone	First	31	61 (47-88)	NR	NR	97	3	NR	65
	Letrozole + trastuzumab		26	61.5 (39-87)	NR	NR	100	0	NR	31
Schwarzberg[42], Johnston[5]; 2003-2006	Letrozole + placebo	First	108	59 (45-87)	0	100	96.3	0	47	57
	Letrozole + lapatinib		111	60 (44-85)	0	100	91.9	0	55	54
Kaufman[6]; 2001-2004; TANDEM	Anastrozole alone	First	104	54 (27-77)	0	100	100	0	59.6	66.3
	Trastuzumab + anastrozole		103	56 (31-85)	0	100	100	0	53.4	60.2
Endocrine therapy ± mTOR inhibitors										
Phase II										
Bachelot[43]; GINECO-TAMRAD	Tamoxifen	First	57	66 (42-86)	0	100	100	93	56	42
	Tamoxifen + everolimus		54	63 (41-81)	0	100	100	98	82	70

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Table 2. Study Characteristics (continued)

Source	Treatment Arm	Treatment Line	No. of Patients	Patient Characteristics			Disease Characteristics (%)		Previous Therapy (%)	
				Median (range) Age (years)	Menopausal Status (%)		HR Positive	HER2 Negative	Chemotherapy	Endocrine
					Pre	Post				
Phase III										
Wolff[44] ; HORIZON	Letrozole + placebo	First	555	63 (28-91)	0	100	95	47	59	40
	Letrozole + temsirolimus		555	63 (36-98)	0	100	96	40	65	43
Piccart[45], Yardley[50], Baselga[4]; 2009-2011; BOLERO-2	Exemestane + placebo	Second	239	61 (28-90)	0	100	100	100	NR	84
	Everolimus + exemestane		485	62 (34-93)	0	100	100	100	NR	84
Endocrine therapy ± CDK 4/6 inhibitors										
Phase II										
Finn[7]; PALOMA-1	Letrozole alone	First	81	64 (38-84)	0	100	100	0	37	28
	Letrozole + palbociclib†		84	63 (41-89)	0	100	100	0	34	27
Phase III										
Turner[17]; PALOMA-3	Fulvestrant + placebo	≥ Second	171	57 (30-88)	20.7	79.3	100	0	30.8	100
	Fulvestrant + palbociclib		347	56 (29-80)	20.7	79.3	100	0	36.2	100
Endocrine ± novel agents										
Endocrine therapy ± RET, VEGFR, and EGFR TKI										
Phase II										
Clemons[46]; OCOG-Zamboney	Fulvestrant + placebo	First	68	59	NR	NR	NR	NR	18	73
	Fulvestrant + vandetanib‡		61	59	NR	NR	NR	NR	18	73
Endocrine therapy ± IGFR antibody										
Phase II										
Robertson[47]	Fulvestrant or exemestane + placebo	Second	50	62 (55-66)	0	100	94	98	64	100
	Fulvestrant or exemestane + ganitumab§		106	61 (54-70)	0	100	98	93	67	100
Endocrine therapy ± VEGF antibody										
Phase III										
Martin[48]; 2007-2011; LEA	Letrozole or fulvestrant	First	166	NR	0	100	100	0	47.8	51.6
	Letrozole or fulvestrant + bevacizumab‖		168	NR	0	100	100	0	43.2	52.6
Dickler[49]; CALGB 40503	Letrozole	First	170	59 (29-87)	NR	NR	100	5	NR	NR
	Letrozole + bevacizumab		173	56 (25-85)	NR	NR	100	3	NR	NR
Endocrine therapy ± HDAC inhibitor										
Phase II										
Yardley[50]; ENCORE	Exemestane + placebo	Second	66	62 (37-88)	0	100	98	89	42	86
	Exemestane + entinostat¶		64	63 (37-85)	0	100	98	92	34	84

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Table 2. Study Characteristics (continued)

Source	Treatment Arm	Treatment Line	No. of Patients	Patient Characteristics: Median (range) Age (years)	Patient Characteristics: Menopausal Status (%) Pre	Patient Characteristics: Menopausal Status (%) Post	Disease Characteristics (%): HR Positive	Disease Characteristics (%): HER2 Negative	Previous Therapy (%): Chemotherapy	Previous Therapy (%): Endocrine
Endocrine therapy ± pan-PI3K inhibitor										
Phase II										
Krop[51]	Fulvestrant + placebo	Second	79	63 (40-82)	0	100	100	0	19	100
	Fulvestrant + pictilisib		89	60 (36-90	0	100	100	0	24	100
Phase III										
Baselga[52]	Fulvestrant + placebo	Second	571	61 (31-90)	0	100	100	0	31	100
	Fulvestrant + buparlisib		576	62 (29-90)	0	100	100	0	24.5	100

NOTE. Data Supplement 7 provides details on regimens used in each study. Chemotherapy was administered in the metastatic setting.

Abbreviations: CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; GINECO, Groupe d'Investigateurs Nationaux pour l'Étude des Cancers Ovariens; HDAC, histone deacetylase; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IGFR, insulin-like growth factor receptor; mTOR, mammalian target of rapamycin; NR, not reported; OCOG, Ontario Clinical Oncology Group; PI3K, phosphatidylinositol 3-kinase; RET, rearranged during transfection; SBCG, Spanish Breast Cancer Group; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

*AZD8931: pan-ErbB TKI (EGFR, HER2, ErbB3).

†Palbociclib: CDK 4/6 TKI.

‡Vandetanib: RET, VEGFR, and EGFR TKI.

§Ganitumab: IGFR antibody (inhibits IGFR).

‖Bevacizumab: VEGF antibody.

¶Entininostat: HDAC TKI.

Table 3. Efficacy Outcomes

Source	Intervention or Comparison	Treatment Line	No. of Patients Evaluated	Survival (months)		CBR (%)*	Time to Initiation of Chemotherapy
				OS	PFS or TTP		
Single-agent *v* single-agent hormone therapies							
Phase II							
Llombart-Cussac[23]; SBCG 2001/03	Exemestane	First	47	Median, 19.9	Median TTP, 6.1	59.6	NR
	Anastrozole		50	48.3	12.1	68	NR
P				NS	NS		
Robertson[14,15]; FIRST	Fulvestrant	First	102	Median, 54.1 (n = 86)	Median TTP, 23.4	72.5	NR
	Anastrozole		103	48.4 (n = 84)	13.1	67.0	NR
P				**.041**	**.01**	.386 (primary end point)	
Ohno[24]; FINDER-1	Fulvestrant (250 mg/month)	Second	45	NR	Median TTP, 6.0	42.2	NR
	Fulvestrant (250 mg + 500 mg on day 0, 250 mg on days 14 and 28, and monthly thereafter)		51	NR	7.5	54.9	NR
	Fulvestrant (500 mg per month + 500 mg on day 14 of month 1)		47	NR	6.0	46.8	NR
Pritchard[25]; FINDER-2	Fulvestrant (250 mg per month)	Second	47	NR	Median TTP, 3.1	31.9	NR
	Fulvestrant (250 mg + 500 mg on day 0, 250 mg on days 14 and 28, and monthly thereafter)		50	NR	6.1	47.1	NR
	Fulvestrant (500 mg per month + 500 mg on day 14 of month 1)		46	NR	6.0	47.8	NR
Phase III							
Di Leo[21,36]; CONFIRM	Fulvestrant 250 mg	Second	374	**Median, 22.03**	**Median PFS, 5.5**	39.6	NR
	Fulvestrant 500 mg		362	**26.4**	**6.5**	45.6	NR
P				**< .05**	**< .05**	NS	
Iwata[22]	Exemestane	First	147	Median, not reached	Median, 13.8 (range, 10.8-16.5)	75 (range, 66.7-82.1)	NR
	Anastrozole		145	60.1	11.1(range, 10.8-16.6)	77.3 (range, 69.1-84.3)	NR
P				NS	NS		
Xu[26]	Fulvestrant	Second	121	NR	Median TTP, 3.6	48.2	NR
	Anastrozole		113	NR	5.2	36.1	NR
P					NS		
Chia[20]; EFECT	Fulvestrant	Second	351	NR	Median PFS, 3.7	32.2	NR
	Exemestane		342	NR	3.7	31.5	NR
P					NS	NS	
Paridaens[37]	Exemestane	First	182	1 year, 86%; Median, 37.2	1-year PFS, 41.7%; Median, 9.9	NR	NR
	Tamoxifen		189	82%; 43.3	31.2%; 5.8	NR	NR
P				NS	NS		
Single-agent *v* combination endocrine therapies							
Phase II							
Johnston[38]; SoFEA	Fulvestrant + placebo	Second	231	19.4 (A *v* B)	4.8 (A *v* B)	NR	NR
	Fulvestrant + anastrozole		243	Median, 20.2	Median PFS, 4.4	NR	NR
P				NS	NS		
	Exemestane		249	21.6 (B *v* C)	3.4 (B *v* C)	NR	NR
P				NS	NS		

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Table 3. Efficacy Outcomes (continued)

Source	Intervention or Comparison	Treatment Line	No. of Patients Evaluated	Survival (months)		CBR (%)*	Time to Initiation of Chemotherapy
				OS	PFS or TTP		
Phase III							
Bergh[13]; FACT	Anastrozole alone	First	256	38.2	10.2	NR	NR
	Fulvestrant + anastrozole		258	Median, 37.8	Median TTP, 10.8	NR	NR
P				NS	NS		
Mehta[12]; SWOG 0226	Anastrozole alone → fulvestrant	First	345	**Median, 41.3**	**PFS, 13.5**	70	NR
	Anastrozole + fulvestrant		349	**47.7**	**15**	73	NR
P				**.05**	**.05**		
Endocrine therapy ± HER2-targeted therapies							
Phase II							
Johnston[39]; MINT	Placebo	First	121	90%	14.0	NR	NR
	Anastrozole + AZD8931 20 mg		118	83%	10.9	NR	NR
	Anastrozole + AZD8931 40 mg		120	87%	13.8	NR	NR
P				NS	NS		
Phase III							
Burstein[40]; CALGB 40302	Fulvestrant + placebo	First	145	Median, 26.4	Median, 3.8	NR	NR
	Fulvestrant + lapatinib		146	30	4.7	NR	NR
P				NS	NS		
Huober[41]; eLEcTRA	Letrozole alone	First	31	NR	3.3	39	NR
	Letrozole + tratuzumab		26	NR	TTP, 14.1	65	NR
P				NS	NS	.06	
Schwarzberg[42] Johnston[5]	Letrozole + placebo	First	108	Median, 32.3	**Median PFS, 3.0**	**29**	NR
	Letrozole + lapatinib		111	33.3	**8.2**	**48**	NR
P				NS	**< .05**	**< .05**	
Kaufman[6]; TAnDEM	Anastrozole alone	First	104	Median, 23.9	**PFS, 2.4 (range, 2-4.6)**	**27.9 (range, 19.5-37.5)**	NR
	Trastuzumab + anastrozole		103	28.5	**4.8 (range, 3.7-7.0)**	**42.7 (range, 33-52.9)**	NR
P				NS	**< .05**	**< .05**	
Endocrine therapy ± mTOR inhibitors							
Phase II							
Bachelot[43]; GINECO	Tamoxifen	First	57	**Median not yet reached**	**Median TTP, 4.5**	**42**	NR
	Tamoxifen + everolimus		54	**32.9**	**8.6**	**61**	NR
P				**< .05**	**< .05**	**< .05**	
Phase III							
Wolff[44]; HORIZON	Letrozole + placebo	First	555	NR	Median, 9.0	NR	NR
	Letrozole + temsirolimus		555	Median, NR	8.9	NR	NR
P				NS	NS		
Piccart[45] Yardley[50] Baselga[4]; BOLERO-2	Exemestane + placebo	Second	239	26.2	**Median PFS, 3.2**	**25.5**	NR
	Everolimus + exemestane		485	31.0	**7.4**	**50.5**	NR
P				.14	**< .05**	**< .05**	
Endocrine therapy ± CDK 4/6 inhibitor							
Phase II							
Finn[7]; PALOMA-1	Letrozole alone	First	81	33.3	10.2	58	NR
	Letrozole + palbociclib		84	37.5	20.2	81	NR
P				.42	**< .001**	**< .001**	

(continued on following page)

Table 3. Efficacy Outcomes (continued)

Source	Intervention or Comparison	Treatment Line	No. of Patients Evaluated	Survival (months)		CBR (%)*	Time to Initiation of Chemotherapy
				OS	PFS or TTP		
Phase III							
Turner[17]; PALOMA-3	Fulvestrant + placebo	≥ Second	171	NR	3.8	19	NR
	Fulvestrant + palbociclib		347	NR	9.2	34	NR
P					**< .001**	**< .001**	
Endocrine therapy ± novel agents							
Endocrine therapy ± RET, VEGFR, and EGFR TKI							
Phase II							
Clemons[46]; OCOG-Zamboney	Fulvestrant + placebo	First	68	69.1%	4.8	NR	NR
	Fulvestrant + vandetanib		61	73.7%	6	NR	NR
P				NS	NS		
Endocrine therapy ± IGFR antibody							
Phase II							
Robertson[47]	Placebo + fulvestrant or exemestane	Second	50	Not reached	5.7	NR	NR
	Ganitumab + fulvestrant or exemestane		106	22.2 months	Median PFS, 3.9	NR	NR
P				**.025** (favors placebo)	NS		
Endocrine therapy ± VEGF antibody							
Phase III							
Martin[48]; LEA	Letrozole or fulvestrant	First	184	51.8	14.4	67.4	NR
	Letrozole or fulvestrant + bevacizumab		190	52.1	19.3	76.8	NR
P				NS	NS	**.041**	
Dickler[49]; CALGB 40503	Letrozole	First	170	44	16	62	NR
	Letrozole + bevacizumab		173	47	20	80	NR
P				NS	**.016**	**.005**	
Endocrine therapy ± HDAC inhibitor							
Phase II							
Yardley[50]; ENCORE	Exemestane + placebo	Second	66	**Median PFS, 19.8**	Median, 2.3	25.8	NR
	Exemestane + entinostat		64	**28.1**	4.3	28.1	NR
P				**< .05**	NS	NS	
Endocrine therapy ± pan-PI3K inhibitor							
Phase II							
Krop[51]	Fulvestrant + placebo	Second	79	NR	5.1	6.3 (ORR)	NR
	Fulvestrant + pictilisib		89	NR	6.6	7.9	NR
P					NS		
Phase III							
Baselga[52]	Fulvestrant + placebo	Second	571	NR	**5.0 (range, 4.0-5.2)**	7.7 months (ORR)	NR
	Fulvestrant + buparlisib		576	NR	**6.9 (range, 6.8-7.8)**	11.8 months	NR
P					**< .001**		

Abbreviations: CBR, clinical benefit rate; CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; GINECO, Groupe d'Investigateurs Nationaux pour l'Étude des Cancers Ovariens; HDAC, histone deacetylase; HER2, human epidermal growth factor receptor 2HR, hormone receptor; IGFR, insulin-like growth factor receptor; mTOR, mammalian target of rapamycin; NR, not reported; NS, not significant; ORR, overall response rate; OS, overall survival PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; RET, rearranged during transfection; TKI, tyrosine kinase inhibitor; TTP, time to progression; VEGFR, vascular endothelial growth factor receptor.

*CBR is defined as the number of patients with complete response, partial response, and stable disease.

assigned to exemestane with everolimus or exemestance with placebo at a ratio of two to one, Piccart et al[45] reported benefits in PFS (7.4 *v* 3.2 months; $P < .05$) and CBR (50.5% *v* 25.5%; $P < .05$) in favor of exemestane with everolimus. There was no statistically significant improvement in OS (31 *v* 26.6 months; $P = .14$).[45]

Endocrine therapy with or without a CDK 4/6 TKI. In a phase II first-line trial in which 165 patients were randomly assigned to letrozole with palbociclib or letrozole alone, Finn et al[7] detected a median PFS benefit (20.2 *v* 10.2 months; $P < .001$) in favor of the combination arm. CBR and ORR were also improved in patients receiving palbociclib. There was no difference in OS (37.5 *v* 33.3 months; $P = .42$). In a phase III trial in the second-line setting or greater in which 521 patients were randomly assigned at a ratio of two to one to fulvestrant with palbociclib or placebo, Turner et al[17] reported significant improvements in PFS (9.2 *v* 3.8 months; $P < .001$) and CBR (34% *v* 19%; $P < .001$) in favor of the palbociclib arm. At the time of this report, OS data were immature.

Endocrine therapy with or without an IGFR antibody. In a phase II second-line trial in which 156 patients were randomly assigned to ganitumab plus either fulvestrant or exemestane compared with placebo plus either fulvestrant or exemestane, Robertson et al[47] detected a decrease in OS with ganitumab-based therapy (HR = 1.78; 80% CI, 1.27 to 2.50; $P = .025$).

Endocrine therapy with or without an HDAC TKI. In a phase II second-line trial in which 130 patients were randomly assigned to exemestane with entinostat or exemestane alone (plus placebo), Yardley et al[50] detected a median survival benefit (28.1 *v* 19.8 months; $P < .05$) in favor of the combination arm, although no difference was detected for either PFS or CBR.

Endocrine therapy plus a pan-PI3K inhibitor. In a phase III second-line trial in which 1,147 patients were randomly assigned to fulvestrant with either placebo or buparlisib, Baselga et al[52] reported a modest benefit in PFS (5 *v* 6.9 months; $P < .001$) in favor of fulvestrant with buparlisib.

QoL

Data on QoL are listed in Table 4 for the four trials[17,20,21,50] that reported QoL outcomes. In general, too few clinical trials in this area incorporate appropriate patient-reported outcomes (PROs) using suitable measures. Many use PRO or QoL measures more suited for assessment in early breast cancer. Many of the data are collected from subgroups of patients and incompletely reported. The analyses used in studies that have incorporated QoL as an outcome are often rather unsophisticated, reporting mean values between groups rather than responder analyses, and none seem to have considered clinically meaningful differences. Consequently, the patient-perceived impact on QoL is not well known. Evaluation of toxicities with the Common Terminology Criteria for Adverse Events does not provide sufficient insight into the risk-versus-benefit experience for the patient. It is recommended that PRO measures be used (eg, PRO version of Common Terminology Criteria for Adverse Events or Functional Assessment of Cancer Therapy), along with relevant treatment-related symptom subscales (eg, subscales for biologic modifiers, TKIs, and endocrine symptoms). A listing of suitable measures can be found at http://www.facit.org. It is important that PROs be included in therapeutic clinical trials to understand the impact of treatment on QoL.

Adverse Events

Data on several key adverse events are listed in Table 5. Because all outcomes are summarized in detail in Table 5, only trials that detected a significant difference for any of the outcomes of interest will be described here, separated by comparison. Distinctive adverse effects of hormone therapy combined with targeted agents are noted here. Clinicians and patients should consider toxicity profiles when deciding on therapeutic options.

Single-agent versus combination endocrine therapies. In a phase III first-line trial in which 311 patients were randomly assigned to anastrozole alone or fulvestrant with anastrozole, Bergh et al[13] noted significantly more hot flashes associated with the combination arm (24.6% *v* 13.8%; $P < .05$).

Endocrine therapy with or without HER2-targeted therapies. In a phase III trial in which 291 patients previously treated with an AI were randomly assigned to fulvestrant with lapatinib or fulvestrant alone (with placebo), Burstein et al[40] reported significantly higher grade 3 adverse effects associated with the combination arm (19% *v* 5%; $P < .05$), and a higher number of patients had to stop treatment early because of adverse effects in the combination arm as well (12% *v* 2%; $P < .05$).

Endocrine therapy with or without mTOR inhibitors. Baselga et al[4,45,56] reported significantly higher grade 3 stomatitis (8% *v* < 1%), fatigue (4% *v* 1%), pneumonitis (3% *v* 0%), and hyperglycemia (5% *v* < 1%) and Rugo et al[54,55] reported a higher discontinuation rate because of adverse events in those receiving everolimus compared with placebo in combination with exemestane (9% *v* 3%).

Endocrine therapy with or without CDK 4/6 inhibitors. Turner et al[17] reported significantly higher grade 3 to 4 neutropenia (62% *v* 0.6%), without an increase in febrile neutropenia, in patients receiving palbociclib in combination with letrozole compared with those receiving placebo and letrozole.

Endocrine therapy plus a pan-PI3K inhibitor. Baselga et al[52] reported significantly higher grade 3 to 4 rash (7.9% *v* 0%), liver enzyme elevation (AST, 18% *v* 2.8%; ALT, 25.5% *v* 1.1%), hyperglycemia (15.4% *v* 0.2%), anxiety (5.4% *v* 0.9%), and depression (4.4% *v* 0.4%) in patients receiving buparlisib in combination with fulvestrant compared with those receiving placebo and fulvestrant.

RECOMMENDATIONS

CLINICAL QUESTION 1

Is there an optimal (defined throughout this guideline as treatments with demonstrated benefits in both treatment-related and quality-of-life outcomes) first-line endocrine therapy regimen for HR-positive metastatic breast cancer?

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

Table 4. QoL

Source	Intervention or Comparison	Treatment Line	No. of Patients Evaluated	QoL Instrument	Summary Score	Subscale Summary Score
Single-agent *v* single-agent hormone therapies						
Phase III						
Di Leo[21,53]; CONFIRM	Fulvestrant 250 mg	Second	374	FACT-B	NR	NR
	Fulvestrant 500 mg		362	TOI	NR	NR
P					NS	
Chia[20]; EFECT	Fulvestrant	Second	NR	FACT-ES	NR	NR
	Exemestane		NR	TOI	NR	NR
P					NS	
Endocrine therapy ± mTOR inhibitors						
Phase III						
Yardley[50]; BOLERO-2	Exemestane	Second	239	EORTC QLQ-C30, QLQ-BR23	NR	Emotional and/or social TTD, 13.8 → 9.5; −4.3
	Everolimus + exemestane		485		NR	13.9 → 11.5; −2.4
P						NS
Endocrine therapy ± CDK 4/6 inhibition						
Phase III						
Turner[17]; PALOMA-3	Fulvestrant + placebo	≥ Second	171	EQ-5D, EORTC QLQ-C30	−4.0*	Emotional, −1.9†
	Fulvestrant + palbociclib		347	EORTC QLQ-BR23	−0.9	2.7
P					**.03**	**.002**

Abbreviations: CDK, cyclin-dependent kinase; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer 30; EORTC QLQ-BR23, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer 23; EQ-5D, EuroQol Group Five-Dimension Self-Report Questionnaire; FACT-B, Functional Assessment of Cancer Therapy–Breast; FACT-ES, Functional Assessment of Cancer Therapy–Endocrine Symptoms; mTOR, mammalian target of rapamycin; NR, not reported; NS, not significant; QoL, quality of life; TOI, trial outcome index; TTD, time to definitive deterioration.

*Mean overall change from baseline in QLQ-C30 score.

†Mean change from baseline (score, 0 to 100).

Question 1.1

For postmenopausal women: What are the optimal sequence and duration?

Recommendation 1.1

Postmenopausal women with HR-positive MBC should be offered AIs as first-line endocrine therapy (Fig 1) (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statements. Treatment decisions must take into account exposure to adjuvant endocrine therapy. There is no survival difference between patients treated with AIs or tamoxifen in randomized controlled trials. Stronger evidence exists for nonsteroidal AIs (eg, letrozole or anastrozole) compared with steroidal AIs (eg, exemestane) in the first-line setting. This recommendation includes patients without prior exposure to AIs or those experiencing relapse > 12 months after completing adjuvant AI therapy. There is insufficient evidence to recommend fulvestrant in the first-line setting (defined as 500 mg every 2 weeks for three doses followed by 500 mg administered once per month [ie, optimal dose and schedule of fulvestrant]); a prospective study is ongoing. Emerging data on targeted agents must be taken into consideration.

Literature review and analysis. Previous studies compared AIs with tamoxifen as first-line therapy for metastatic disease.[32,37,57-59] AIs generally resulted in improved PFS or TTP without having an impact on OS. A meta-analysis[30] concluded that tamoxifen and toremifene were similar in efficacy, with some differences in reported adverse events.

One small phase II trial and one placebo-controlled phase III trial[22] compared single-agent anastrozole with exemestane in the first-line setting. Although TTP was numerically longer with anastrozole in the phase II trial, this difference was not significant. The phase III trial demonstrated similar TTP, overall response, and OS, and both agents were well tolerated.

The phase II FIRST trial[14] compared anastrozole with fulvestrant at a 250-mg dose followed by 500 mg (500 mg on days 0, 14, and 28, then 500 mg every 28 days) in the first-line setting.[14] The primary end point of this trial was CBR, which was similar between the two arms. With longer follow-up, fulvestrant was associated with a significant improvement in TTP, without an increase in toxicity. On the basis of these data, survival was added as a secondary end point by amendment, although some patients were lost to follow-up and were censored at the time of last contact. OS was improved in patients treated with fulvestrant[15] (Table 3); the phase III FALCON trial (Data Supplement 7; ClinicalTrials.gov identifier NCT01602380) is comparing these treatments.

Two trials compared the combination of fulvestrant and the nonsteroidal AI anastrozole with anastrozole alone in the first-line metastatic setting, with opposing results. The FACT (Fulvestrant and Anastrozole Combination Therapy) trial[13] found no impact on

Table 5. Acute Adverse Events

Source	Intervention or Comparison	Treatment Line	No. of Patients Evaluated	Grade 3 to 4 Adverse Event (%)																	
				TRM	Bone Pain	Hypercalcemia	Rashes	Hot Flashes	Thromboembolism	Uterine Bleeding	Nausea	Vomiting	Diarrhea	Infections	Fatigue	Hypertension	Cardiomyopathy	Pulmonary Toxicity	Neutropenia	Stomatitis	Anemia	Alopecia	Peripheral Neuropathy
Single-agent *v* single-agent hormone therapies																							
Phase II																							
Llombart-Cussac[23]; SBCG 2001/03	Exemestane	First	51	—	3.9	—	—	—	—	—	—	—	—	5.9	—	7.8	—	—	—	—	—	—	—
	Anastrozole		52	—	7.7	—	—	—	—	—	—	—	—	1.9	—	0	—	—	—	—	—	—	—
Phase III																							
Di Leo[21,36]; CONFIRM	Fulvestrant 250 mg	Second	374	1	—	—	—	0	0.6	0.3	—	< 1	—	—	—	—	0	—	—	—	< 1	—	—
	Fulvestrant 500 mg		362	< 2	—	—	—	0	1.1	0.3	—	< 1	—	—	—	—	0.8	—	—	—	< 1	—	—
Iwata[22]	Exemestane	First	136	—	—	—	—	0	—	—	—	—	—	—	0	1	—	—	—	—	—	—	—
	Anastrozle		131	—	—	—	—	0	—	—	—	—	—	—	0	1	—	—	—	—	—	—	—
Xu[26]*	Fulvestrant	Second	121	1	—	—	—	4	—	—	7	—	—	—	—	—	—	—	—	—	—	—	—
	Anastrozole		113	4	—	—	—	3	—	—	2	—	—	—	—	—	—	—	—	—	—	—	—
Chia[20]; EFECT†	Fulvestrant	Second	351	0	—	—	—	8.8	—	—	6.8	—	3.4	—	6.3	—	—	—	—	—	—	2.3	—
	Exemestane		340	0				11.5			7.9	—	2.9	—	10	—	—	—	—	—	—	1.5	—
Paridaens[37]	Exemestane	First	182	—	3.8	—	—	0.5	—	—	0	0	0	1.1	1.1	3.3	2.1	—	1.1	—	1.1	0	—
	Tamoxifen		189	—	5.8	—	—	0	—	—	0.5	0	0	0	1.1	3.2	1.6	—	0	—	1.1	0	—
Single-agent *v* combination endocrine therapies																							
Phase II																							
Johnston[39]; SoFEA	Fulvestrant + placebo	First	230	—	1	—	0	2	—	—	1		1	0	1	< 1	—	—	—	—	< 1	0	< 1
	Fulvestrant + anastrozole		241	—	1	—	0	1	—	—	2		< 1	0	< 1	1	—	—	—	—	0	0	0
	Exemestane		247	—	1	—	0	< 1	—	—	3		0	0	0	0	—	—	—	—	1	0	0
Phase III																							
Bergh[13]; FACT	Anastrozole alone	First	156	5	—	—	—	**13.8**	1.6	—	—	—	—	—	—	—	—	1	—	—	—	—	—
	Fulvestrant + anastrozole		155	11	—	—	—	**24.6**	2.3	—	—	—	—	—	—	—	—	0	—	—	—	—	—
Endocrine therapy ± HER2-targeted therapies																							
Phase II																							
Johnston[39]; MINT	Placebo	First	121	—	—	—	2	—	—	—	—	—	—	—	—	2	—	—	—	—	—	—	—
	Anastrozole + AZD8931 20 mg		118	—	—	—	0	—	—	—	—	—	—	—	—	3	—	—	—	—	—	—	—
	Anastrozole + AZD8931 40 mg		120	—	—	—	8	—	—	—	—	—	—	—	—	3	—	—	—	—	—	—	—
Phase III																							
Burstein[40]; CALGB 40302	Fulvestrant + placebo	First	145	—	—	—	0	0	—	—	—	—	0	—	1	—	—	—	—	0‡	—	—	—
	Fulvestrant + lapatinib		146	—	—	—	3	1	—	—	—	—	8	—	3	—	—	—	—	1‡	—	—	—
Huober[41]; eLEcTRA	Letrozole alone	First	31	—	6.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Letrozole + tratuzumab		26	—	3.8	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Schwarzberg[42], Johnston[5]	Letrozole + placebo	First	106	—	0	—	0	0	—	—	< 1	0	0	—	0	—	—	—	—	—	—	0	—
	Letrozole + lapatinib		113	—	< 1	—	0	0	—	—	0	< 1	7	—	4	—	—	—	—	—	—	0	—
Kaufman[6]; TAnDEM	Anastrozole alone	First	104	—	0	—	—	—	—	—	0	1	0	—	0	3.8	1	—	—	—	—	—	—
	Trastuzumab + anastrozole		103	—	1.9	—	—	—	—	—	1	2.9	1	—	1	1.9	1	—	—	—	—	—	—
Endocrine therapy ± mTOR inhibitors																							
Phase II																							
Bachelot[43]; GINECO	Tamoxifen	First	57	—	—	—	0	0	—	—	0	4	0	5	11	—	—	4	—	0	—	—	—
	Tamoxifen + everolimus		54	—	—	—	4	0	—	—	4	0	2	7	6	—	—	2	—	6	—	—	—

(continued on following page)

Table 5. Acute Adverse Events (continued)

Source	Intervention or Comparison	Treatment Line	No. of Patients Evaluated	Grade 3 to 4 Adverse Event (%)																		
				TRM	Bone Pain	Hypercalcemia	Rashes	Hot Flashes	Thromboembolism	Uterine Bleeding	Nausea	Vomiting	Diarrhea	Infections	Fatigue	Hypertension	Cardiomyopathy	Pulmonary Toxicity	Neutropenia	Stomatitis	Anemia	Alopecia	Peripheral Neuropathy
Phase III																						
Wolff[64]	Letrozole + placebo	First	553	—	—	< 1	—	—	—	—	1	1	1	1	—	—	—	—	—	< 1	1	—	—
	Letrozole + temsirolimus		550	—	—	1	—	—	—	—	1	1	2	1	—	—	—	—	—	1	1	—	—
Yardley[50], Rugo[54], Baselga[4]; BOLERO-2	Exemestane + placebo	Second	238	—	—	—	0	—	—	—	1	< 1	1	—	1	—	—	0	—	1	< 2	—	—
	Everolimus + exemestane		482	—	—	—	1	—	—	—	< 2	< 2	< 3	—	< 4	—	—	3	—	8	6	—	—
Endocrine therapy ± CDK 4/6 inhibitor																						
Phase II																						
Finn[7]	Letrozole	First	77	—	0	—	—	0	—	—	1	1	0	—	1	—	—	—	1	0	1	—	—
	Letrozole + palbociclib		83	—	1	—	—	0	—	—	2	0	4	—	4	—	—	—	54	0	6	—	—
Phase III																						
Turner[17]	Fulvestrant	≥ Second	171	—	—	—	—	0	—	—	6	6	6	—	1.2	—	—	—	0.6	0	1.7	—	—
	Fulvestrant + palbociclib		347	—	—	—	—	0	—	—	0	3	0	—	2	—	—	—	62	6	2.6	—	—
Endocrine therapy ± novel agents																						
Endocrine therapy ± antiangiogenic agents																						
Phase II																						
Robertson[47]	Placebo + fulvestrant or exemestane	Second	49	—	—	—	—	—	—	—	0	0	0	—	0	—	—	—	1	—	—	—	—
	Ganitumab + fulvestrant or exemestane		106	—	—	—	—	—	—	—	2	2	1	—	2	—	—	—	6	—	—	—	—
Martin[48]; LEA	Letrozole or fulvestrant	First	184	0	—	—	—	—	0	—	—	0	1	—	0	3	—	—	0	—	1	—	—
	Letrozole or fulvestrant + bevacizumab		190	0.3 (n = 7)	—	—	—	—	2.3	—	—	1	1	—	2	15	—	—	1	—	1	—	—
Dickler[49]	Letrozole	First	170		—	—	—	—	1	—	—	—	—	—	—	2	—	—	—	—	—	—	—
	Letrozole + bevacizumab		173		—	—	—	—	2	—	—	—	—	—	—	22	—	—	—	—	—	—	—
Endocrine therapy ± emerging agents																						
Phase II																						
Yardley[50]; ENCORE	Exemestane + placebo	Second	66	—	—	—	—	—	—	—	2	0	2	—	3	—	—	—	0	—	4	—	—
	Exemestane + entinostat		64	—	—	—	—	—	—	—	5	5	0	—	13	—	—	—	15	—	2	—	—
Endocrine therapy ± pan-PI3K inhibitor																						
Phase II																						
Krop[51]	Fulvestrant + placebo	Second	79	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Fulvestrant + pictilisib		89	—	—	—	17	—	—	—	3.4	3	7	—	6	—	—	—	—	2	—	—	—
Phase III																						
Baselga[52]	Fulvestrant + pictilisib	Second	571	NR	—	—	—	—	—	—	1.4	—	1.1	—	—	—	—	—	—	0.5	—	—	—
	Fulvestrant + buparlisib		576	NR	—	—	7.9	—	—	—	1.7	—	3.7	—	—	—	—	—	—	2.1	—	—	—

NOTE. Dashes indicate not reported.

Abbreviations: CDK, cyclin-dependent kinase; GINECO, Groupe d'Investigateurs Nationaux pour l'Étude des Cancers Ovariens; HER2, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin; NR, not reported; OCOG, Ontario Clinical Oncology Group; PI3K, phosphatidylinositol 3-kinase; SBCG, Spanish Breast Cancer Group; TRM, treatment-related mortality.

*Reported as ≥ 3% incidence rate.

†Reported as ≥ 2% incidence rate.

‡Reported as mucositis and stomatitis combined.

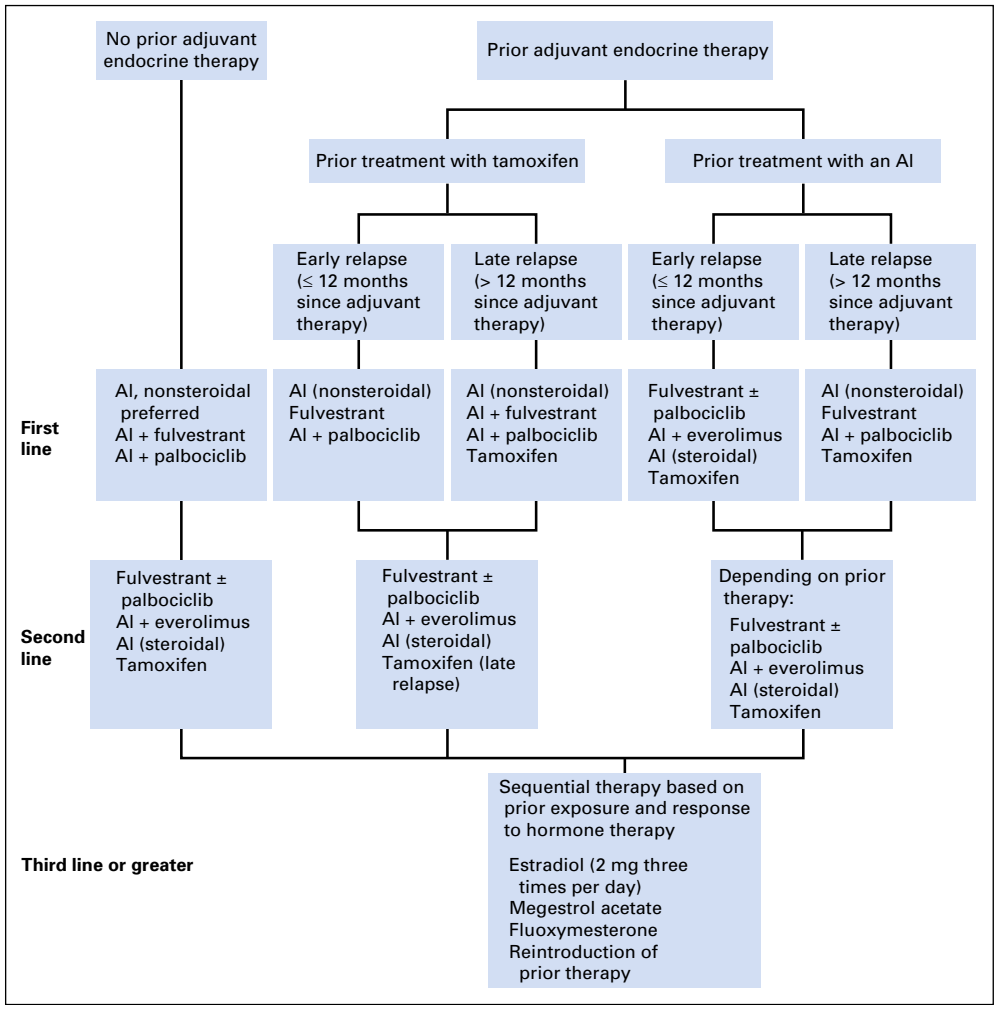

Fig 1. Hormone therapy for postmenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered at 500 mg every 2 weeks for three cycles, then once per month as an intramuscular injection. Withdrawal of tamoxifen or progestins was reported to result in short-term disease responses in older literature. Steroidal indicates exemestane; nonsteroidal indicates anastrozole or letrozole. AI, aromatase inhibitor.

TTP or OS, whereas SWOG 0226[12] found a significant improvement in PFS, with a borderline 6.4-month improvement in OS. Major differences in the trial populations are thought to explain this difference; almost half of the patients in the SWOG trial had de novo metastatic disease, with no prior exposure to adjuvant hormone therapy (ie, tamoxifen). In contrast, > 60% of patients in the FACT trial had received prior endocrine therapy, and < 20% were diagnosed as having de novo metastases. There were no significant toxicity differences between single-agent and combination therapy.

A recent study evaluated the addition of the CDK 4/6 inhibitor palbociclib to the nonsteroidal AI letrozole and demonstrated a significant improvement in PFS, without an improvement in OS.[7] These data led to accelerated FDA approval of this combination in the first-line setting, pending results from an ongoing phase III trial in the same setting.

There were no recent trials comparing chemotherapy with chemotherapy plus concurrent hormone therapy in the treatment of HR-positive metastatic disease. ECOG 3186[10] randomly assigned 231 women to receive chemotherapy or chemotherapy with tamoxifen and fluoxymesterone. This trial included patients with both ER-positive and ER-unknown disease, as well as both post- and premenopausal women. Time to treatment failure (TTF) was similar between the two treatment groups, although in the subset of women with ER-positive disease, TTF was longer in patients receiving combination therapy. There was no difference in OS. Of note, all recent studies have included only postmenopausal women (regardless of age).

Clinical interpretation. In postmenopausal women, AIs may provide better disease control compared with tamoxifen in the first-line setting, without a benefit in OS. Available data suggest that either nonsteroidal or steroidal AIs can be used without differential efficacy.

Toremifene is a reasonable alternative to tamoxifen, with a slightly different toxicity profile and substantially higher cost. Toremifene can be used in conjunction with inhibitors of CYP2D6 and may be an option in some women receiving such inhibitors (eg, fluoxetine).

Although results from the FIRST trial are encouraging, definitive data from an ongoing phase III trial will be required (Data Supplement 7; ClinicalTrials.gov identifier NCT01602380) to understand the potential differences in efficacy between fulvestrant (at the currently approved dose) and AIs.

It is reasonable to combine palbociclib with an AI as first-line therapy, because this combination prolongs PFS. Phase III data are expected in 2016. Toxicity, the need for monthly blood counts, and drug access must be taken into account in making this decision.

Treatment should be administered until disease progression is documented by imaging, examination, or symptoms. Care should be taken in the interpretation of bone imaging and serum tumor

markers, because results may be misleading. Withdrawal responses have been observed in patients after long periods of disease control with hormone therapy.

Question 1.2

Should hormone therapy be administered in combination with other hormonal agents or chemotherapy?

Recommendation 1.2

Combination hormone therapy with fulvestrant, with a loading dose followed by 500 mg every 28 days, plus a nonsteroidal AI may be offered to patients with MBC without prior exposure to adjuvant endocrine therapy (Fig 1) (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Qualifying statements. The recommendation for combination therapy in patients treated in the first-line setting without prior exposure to adjuvant hormone therapy (tamoxifen) is on the basis of positive survival results from the SWOG 0226 randomized phase III trial; the greatest benefit in PFS was observed in an unplanned subset analysis of approximately 400 patients who had no prior exposure to hormone therapy. A similar study showed no benefit from combination therapy, but important differences in study design and patient populations existed between the two trials. The use of fulvestrant 500 mg with a loading schedule in combination with anastrozole is being studied in a phase III neoadjuvant trial.[60] There are no ongoing trials studying high-dose fulvestrant in combination with AIs in MBC.

Literature review and analysis. Conflicting data exist regarding the value of first-line combined endocrine therapy with low-dose fulvestrant and a nonsteroidal AI compared with an AI alone. These data are further complicated by the use of low-dose fulvestrant in these trials, because the 500-mg dose was shown to be superior to 250 mg in the trial and is now the approved dose. Benefit from the combination of low-dose fulvestrant and a nonsteroidal AI seems to be limited to patients without prior exposure to hormone therapy for breast cancer or with de novo HR-positive metastatic disease. Ongoing trials are evaluating the combination of high-dose fulvestrant with a nonsteroidal AI.

Older studies compared the combination of chemotherapy and hormone therapy with chemotherapy. A cooperative group trial randomly assigned 231 patients with MBC to cyclophosphamide, doxorubicin, and fluorouracil with or without tamoxifen and fluoxymesterone from 1988 to 1992.[10] The response rate was similar between the two arms. TTF was longer in patients with HR-positive disease receiving chemotherapy plus hormone therapy, but there was no difference in OS.

Clinical interpretation. On the basis of the SWOG 0226 data, the combination of low-dose fulvestrant and an AI could be considered in the unique population of patients with HR-positive MBC without prior exposure to hormone therapy. This recommendation will be affected by the results of ongoing trials evaluating fulvestrant 500 mg and combination studies with targeted agents.

Limited efficacy data do not support a compelling clinical advantage for the use of combined chemotherapy and endocrine therapy. Sequential therapy is preferred.

Question 1.3

For premenopausal women: What is the optimal timing of ovarian suppression or ablation? Should all patients have their ovaries suppressed? What is the best partner hormonal agent in this setting?

Recommendation 1.3

Premenopausal women with HR-positive MBC should be offered ovarian suppression or ablation in combination with hormone therapy. Ovarian suppression with either GnRH agonists or ablation with oophorectomy seems to achieve similar results in MBC. 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 or ablation alone, although combination therapy is preferred (Fig 2). Treatment should be on the basis of the biology of the tumor and the menopausal status of the patient, with careful attention paid to production of ovarian estrogen (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statements. Premenopausal women without prior exposure to hormone therapy should be treated with ovarian suppression and tamoxifen or ovarian suppression and an AI. Tamoxifen alone can also be considered, although available data suggest improved outcomes when ovarian suppression is also used.[18,19] All clinically important trials of endocrine therapy for advanced breast cancer in the past decade have included only postmenopausal women or, less commonly, premenopausal women rendered postmenopausal at the time of study entry. There are no clinically important data in the current era for endocrine therapy for advanced breast cancer in women who remain premenopausal. For that reason, and because of data supporting ovarian suppression as initial therapy for premenopausal women with ER-positive MBC, the panel uniformly recommends that premenopausal women start ovarian suppression. Thereafter, treatment of premenopausal women parallels that of postmenopausal women (Figs 1 and 2).

A discussion between the oncologist and the patient regarding risks and benefits is critical. Premenopausal women who develop metastatic disease while receiving adjuvant tamoxifen or within 12 months of treatment should be treated with ovarian suppression and an AI. Ovarian suppression should be continued during subsequent hormone therapies. Patient choice and clear discussion of options and treatment goals are critical.

Although historic data suggest comparable results with GnRH agonist therapy and surgical oophorectomy,[61] caution should be exercised when GnRH agonists are used, because suppression of ovarian production of estrogen may be incomplete, particularly when combined with AIs or when administered once every 3 months (this schedule is not recommended). Estradiol levels performed with a high-sensitivity assay should be monitored in premenopausal women treated with GnRH agonists and AIs.

Providers should recognize and acknowledge special issues faced by premenopausal women with MBC, including loss of fertility. Although required systemic treatment will preclude pregnancy for most patients, options such as cryopreservation of embryos or oocytes should be discussed, with a careful evaluation of the limitations associated with metastatic disease.

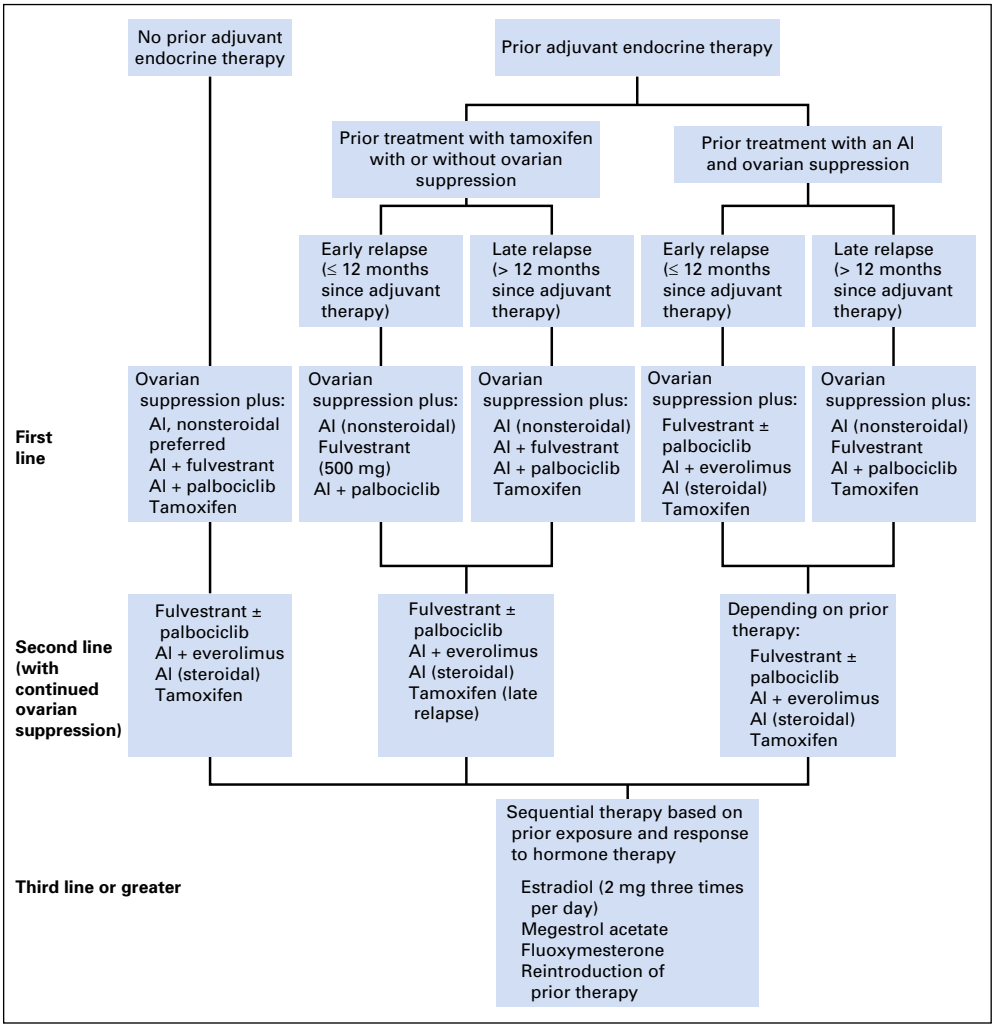

Fig 2. Hormone therapy for premenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered at 500 mg every 2 weeks for three cycles, then monthly as an intramuscular injection. Withdrawal of tamoxifen or progestins was reported to result in short-term disease responses in older literature. Steroidal indicates exemestane; nonsteroidal indicates anastrozole or letrozole. AI, aromatase inhibitor.

Literature review and analysis. There were no recent studies addressing optimal timing of ovarian suppression or the most effective hormone combinations in premenopausal women with MBC. Previous data demonstrated efficacy with ovarian ablation, similar to that seen with tamoxifen.[62] Several small randomized trials and a meta-analysis confirmed the efficacy of tamoxifen in premenopausal women with HR-positive MBC.[63]

Ovarian suppression with GnRH agonists and ovarian ablation resulted in similar outcomes in a phase III trial,[61] leading to widespread use of these agents as treatment of metastatic disease. One study compared a GnRH agonist and tamoxifen with the GnRH agonist or tamoxifen alone as treatment for premenopausal women with MBC,[18] reporting improved response duration and survival with the combination therapy compared with either tamoxifen or the GnRH agonist alone. A meta-analysis of four trials demonstrated improved response, PFS, and OS in patients receiving combination therapy.[19] QoL and toxicity data were not routinely collected.

AIs are contraindicated in premenopausal women, because the reduction in tissue estrogen can lead to increased secretion of gonadotropins, causing compensatory rises in ovarian estrogens and possible induction of ovulation. This issue is most relevant for women who were premenopausal at the time of diagnosis and are now amenorrheic as a result of chemotherapy. Three small nonrandomized trials evaluated the combination of OS and an AI and demonstrated efficacy with varying degrees of ovarian suppression.[64-66] Although not included in the evidence base because of the nature of their trial design (nonrandomized phase II), these three trials[64-66] provide important data that inform the use of hormone therapy in premenopausal women with HR-positive MBC.

Ovarian suppression is required in premenopausal women receiving an AI. However, there are no data defining the optimal level of plasma estradiol, and tests vary widely in sensitivity, resulting in noncomparable results. Inferential data suggesting a relationship between poor plasma suppression of estradiol and worse outcomes in obese women with breast cancer receiving AIs,[64-68] as well as a fundamental consideration of mechanisms of action, suggest that adequate ovarian suppression is important for efficacy in MBC.

Clinical interpretation. Current data suggest that ovarian suppression or ablation in combination with tamoxifen is superior to tamoxifen alone as first-line therapy for premenopausal women. Tamoxifen or ovarian suppression alone can be considered in patients who are naïve to prior hormone therapy.

Ovarian suppression with GnRH agonists is an acceptable alternative to surgical oophorectomy. The combination of

ovarian suppression with AIs can be effective in premenopausal women. Significant caution should be exercised, because ovarian suppression may be incomplete, leading to ovarian production of estrogen. Trials have not routinely measured estradiol, follicle-stimulating hormone, or luteinizing hormone levels to assess the extent of ovarian suppression. Because of the possibility of incomplete ovarian suppression with GnRH agonist therapy, clinicians should be alert to changing patient symptoms that might suggest persistent ovarian function. It may be helpful to confirm ovarian suppression by measuring estradiol level.

Providers should recognize and acknowledge specific issues faced by premenopausal women with MBC, including loss of fertility. Although required systemic treatment will preclude pregnancy for most patients, options such as cryopreservation of embryos or oocytes should be discussed, with a careful evaluation of the limitations associated with metastatic disease.

Question 1.4

Are there demonstrated differences between pre- and postmenopausal patients?

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 (Fig 2) (Type: evidence and consensus based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Qualifying statements. In premenopausal women undergoing ovarian suppression with GnRH agonists in combination with AIs, the AIs may stimulate production of ovarian estrogen. The optimal level of estradiol is unknown; we recommend that the local laboratory definition of menopausal levels of estradiol (using a high-sensitivity assay) be used for this purpose.

CLINICAL QUESTION 2

Is there an optimal second-line or later endocrine therapy for HR-positive MBC?

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

Question 2.1

Should other treatment or disease-free interval play a role in treatment selection?

Recommendation 2.1

The choice of second-line hormone therapy should take into account prior treatment exposure and response to previous endocrine therapy (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statements. Lack of benefit with prior endocrine therapy may be associated with poor or short response to subsequent therapy; close monitoring should be considered. Because of inferior efficacy, treatment with the same hormonal agent on or within 12 months of completing adjuvant therapy is not recommended. Emerging data combining hormonal agents with targeted therapy should be considered.

Literature review and analysis. Prior treatment and disease-free interval clearly influence choice of treatment. Patients who develop recurrent disease while receiving adjuvant hormone therapy or within 1 year of completing that treatment are defined as having disease resistant to that specific therapy, but they can respond to sequential hormone therapy. In general, disease that recurs within the first 2 years of adjuvant hormone therapy is generally less responsive to hormone therapy. This information is inferred from older natural history studies.

Clinical trials studying second-line hormone therapy included patients who experienced relapse while receiving adjuvant therapy or shortly after completing treatment. The BOLERO-2 (Breast Cancer Trials of Oral Everolimus) and PALOMA-3 trials defined these patients as those experiencing relapse during or within 12 months after the end of adjuvant treatment with a nonsteroidal AI.[4,17] However, a clear and consistent definition of resistance to adjuvant hormone therapy is lacking, and there are no data to guide the appropriate sequence of therapy in patients on the basis of type of adjuvant treatment. Patients with a short disease-free interval from diagnosis of early-stage disease to relapse and those who experience distant relapse while receiving adjuvant hormone therapy may have shorter responses to subsequent endocrine therapy.

Clinical interpretation. The choice of second-line hormone therapy should take into account agents used in the adjuvant and first-line settings, as well as disease-free interval, response to prior hormone therapy, organ function, and extent of disease (Fig 1). Both exemestane and fulvestrant are reasonable options on the basis of current data.[20,21,31,36] Tamoxifen should also be considered in patients with hormone-responsive disease.

Hormone therapy should be considered after chemotherapy as well. Hormone therapy can be used as primary treatment or maintenance therapy after response or reintroduced after progression with chemotherapy. Sequential hormone therapy should be used as long as the patient seems to be benefitting from hormone treatment and does not have evidence of immediately life-threatening disease or rapid progression of visceral disease while receiving adjuvant hormone therapy.

Clinicians should consider using exemestane combined with the mTOR inhibitor everolimus, on the basis of the results of the BOLERO-2 trial,[4] or fulvestrant combined with the CDK 4/6 inhibitor palbociclib, on the basis of the results of the PALOMA-3 trial.[17] In general, if a tumor has progressed with a specific agent, other agents in that class will not be effective. Examples include letrozole or anastrozole and tamoxifen or toremifene.

Question 2.2

Which hormone therapy should be offered?

Recommendation 2.2

Sequential hormone therapy should be offered to patients with endocrine-responsive disease. Options are shown in Figure 1 (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statements. After progression with a nonsteroidal AI, several options exist, including the combination of exemestane and everolimus, the combination of fulvestrant and palbociclib, or single-agent exemestane or fulvestrant with a loading dose followed by 500 mg administered every 28 days. There was more toxicity associated with the combination of exemestane and everolimus compared with single-agent endocrine options; exemestane plus everolimus resulted in an improvement in PFS without improvement in OS compared with exemestane alone (Figs 1 and 2). There was also more toxicity associated with the combination of fulvestrant and palbociclib compared with single-agent options; fulvestrant plus palbociclib resulted in an improvement in PFS compared with fulvestrant alone; OS data are immature at this time (Figs 1 and 2). Randomized trials have demonstrated similar outcomes when comparing exemestane with fulvestrant at the 250-mg dose, with or without a loading dose.

Sequential hormone therapy should be used as long as the patient seems to be benefitting from hormone treatment and does not show evidence of rapid progression with organ dysfunction. New hormonal agents should not be added to existing therapy at disease progression.

Literature review and analysis. Initial studies of third-generation AIs compared these agents with megestrol acetate in the second-line setting. AIs were superior to megestrol acetate, with reduced toxicity.[31,69]

Several phase II trials compared low-dose fulvestrant (250 mg every 28 days) with anastrozole in the second-line setting and found no difference in PFS or OS, confirming older studies. The phase III EFECT study[20] directly compared exemestane with fulvestrant, with a loading dose followed by low dose (500 mg on day 0, 250 mg on days 14 and 28, then 250 mg every 28 days). PFS was equivalent between the two arms, and both treatments were well tolerated.

Recent studies comparing hormonal agents for MBC have focused on increasing dose and exposure to the selective ER downregulator fulvestrant in an attempt to both achieve steady-state levels earlier and increase plasma levels of the active agent. Two small phase II trials compared fulvestrant with a loading dose followed by high dose (500 mg on days 0, 14, and 28, then 500 mg every 28 days) with fulvestrant with a loading dose followed by low dose (500 mg on day 0, 250 mg on days 14 and 28, then 250 mg every 28 days) with low-dose fulvestrant (250 mg every 28 days)[24,25] and did not observe a difference in PFS. Definitive results were available from the phase III CONFIRM trial,[36,53] which compared fulvestrant with a loading dose followed by low dose with fulvestrant with a loading dose followed by high dose, demonstrating only a 1-month improvement in PFS but a significant 4.1-month improvement in OS, without significant toxicity. This study led to FDA approval of the loading dose followed by high dose regimen.

The SoFEA trial[38] added fulvestrant with a loading dose followed by low dose (500 mg on day 0, 250 mg on days 14 and 28, then 250 mg every 28 days) to anastrozole in women experiencing disease progression with anastrozole and compared the combination with fulvestrant alone plus placebo or with exemestane. There was no difference in PFS when comparing fulvestrant with exemestane or the combination.

Estrogens (estradiol) and progestins (megestrol acetate) have demonstrated efficacy after progression with AIs and tamoxifen.[70,71] Older data suggest that withdrawal of tamoxifen or progestins may result in disease response in patients with hormone-responsive MBC.[72] The value of this approach with current treatment options is unknown.

Clinical interpretation. On the basis of current data, the nonsteroidal AI exemestane and the selective ER downregulator fulvestrant were equally effective in the second-line setting. Fulvestrant should be administered with a loading dose followed by 500 mg intramuscularly each month. This dose resulted in superior survival compared with the 250-mg dose.

The addition of a new hormonal agent to an existing drug that is no longer suppressing cancer growth is not recommended. The inactive agent should be discontinued when there is clear evidence of cancer progression. Additional hormone options for later-line therapy include reintroduction of prior endocrine agents and consideration of progestational agents (eg, megestrol acetate) or estrogens (eg, estradiol). Patients who experience long periods of tumor control with hormone therapy may consider withdrawal of endocrine treatment, because continuous therapy is not always required.

Question 2.3

What are the optimal timing, dose, schedule, and duration of treatment?

Recommendation 2.3

Fulvestrant should be administered using the 500-mg dose and with a loading schedule (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statement. These are the most effective therapeutic dose and schedule for fulvestrant.

Literature review and analysis. The CONFIRM trial demonstrated improved OS with a fulvestrant loading dose followed by high dose (500 mg on days 0, 14, and 18, followed by 500 mg every 28 days) compared with a fulvestrant loading dose followed by low dose (500 mg on day 0, 250 mg on days 14 and 28, then 250 mg every 28 days).[21,36,53] Estradiol at a dose of 2 mg three times per day was as effective as and better tolerated than a higher dose.[71] Use of tumor markers or circulating tumor cells to inform change of treatment did not demonstrate improved survival compared with clinical symptoms, radiographic studies, or physical examination.[73]

Clinical interpretation. A fulvestrant loading dose followed by high dose is the preferred dose and schedule for fulvestrant administration. Estradiol should be used at a dose of 2 mg three times per day. Hormone therapy should be continued until there is clear evidence of disease progression on the basis of clinical symptoms, radiographic studies, or physical examination.

CLINICAL QUESTION 3

How or should endocrine therapies be used in combination or sequence with:

3.1 mTOR inhibitors (everolimus)?
3.2 CDK 4/6 inhibitors (palbociclib)?

Question 3.1

How or should endocrine therapies be used in combination or sequence with mTOR inhibitors?

Recommendation 3.1

Exemestane and everolimus may be offered to postmenopausal women with HR-positive MBC who experience progression during treatment with nonsteroidal AIs, either before or after treatment with fulvestrant, because PFS but not OS was improved compared with exemestane alone. Other options are shown in Figures 1 and 2. This combination should not be offered as first-line therapy for patients who experience relapse > 12 months from prior nonsteroidal AI therapy or for those who are naïve to hormone therapy (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statements. Hormonal therapy should be changed when everolimus is initiated. Limited data support improved clinical benefit from tamoxifen and everolimus in patients with prior exposure to nonsteroidal AIs. The combination of everolimus and a nonsteroidal AI could be considered for patients with prior progression with exemestane, using the general principles of sequential hormone therapy.

Care should be taken in patients with existing hyperglycemia, and patients should be educated about the risks of therapy, including stomatitis and interstitial pneumonitis. Treatment should be individualized, with dose reductions and/or interruptions as indicated.

Literature review and analysis. Two recent randomized trials reported data on the efficacy of the mTOR inhibitor everolimus in combination with hormone therapy.[4,43] Both studies treated patients with previous exposure to the nonsteroidal inhibitor anastrozole or letrozole, with a strict definition of resistance used in the phase III trial for eligibility.

The phase II open-label TAMRAD trial[43] compared tamoxifen with tamoxifen plus everolimus. The primary end point, CBR, was superior in the combination arm. Exploratory analysis of PFS and OS also suggested improved outcomes with everolimus. Toxicity was increased in the combination arm.

BOLERO-2[4] was a phase III double-blind randomized trial comparing exemestane plus everolimus with exemestane plus placebo, using a two-to-one randomization scheme. PFS and CBR were significantly improved in the combination arm, leading to FDA approval of the combination as second-line therapy for HR-positive MBC. There was no statistically significant improvement in OS between the two arms, although there was a numeric difference of 4.4 months.

Toxicity was increased with the addition of everolimus to hormone therapy.[54,55,74] Significant toxicities included stomatitis, fatigue, interstitial pneumonitis (a class effect from rapamycin analogs), and hyperglycemia, among others; more patients discontinued everolimus and exemestane compared with placebo and exemestane because of adverse events. Toxicity was controlled in a majority of patients with dose reductions and interruptions.

The mTOR inhibitor temsirolimus was studied in the first-line setting in the HORIZON trial.[44] Patients were randomly assigned to intermittent dosing of temsirolimus plus letrozole or letrozole plus placebo. The trial was closed early because of futility, with no difference in PFS between the two arms. This finding has been hypothesized to be a result of inadequate dosing of temsirolimus and possibly a less heavily pretreated, AI-naïve population or lack of efficacy.

Clinical interpretation. The combination of exemestane and everolimus should be considered for postmenopausal women with HR-positive MBC who experience progression during or shortly after treatment with nonsteroidal AIs, because the combination resulted in an almost 5-month improvement in PFS compared with exemestane alone. Treatment must take into account the increased toxicity seen with this combination, and careful monitoring with appropriate dose reductions and interruptions is recommended.

Question 3.2

How or should endocrine therapies be used in combination or sequence with CDK 4/6 inhibitors?

Recommendation 3.2

A nonsteroidal AI and palbociclib may be offered to postmenopausal women with treatment-naïve HR-positive MBC; PFS but not OS was improved compared with the nonsteroidal AI letrozole alone. Other options are shown in Figures 1 and 2. The accelerated approval of palbociclib is dependent on results of an ongoing phase III trial in the same setting (Data Supplement 8; PALOMA-2 trial). Results from the PALOMA-2 trial will be presented at the ASCO 2016 Annual Meeting. A press release[74a] confirms that the trial met its primary end point. Letrozole plus palbociclib improved PFS compared with letrozole alone as first-line therapy for HR-positive metastatic breast cancer in postmenopausal women. Survival data are not yet available.

Palbociclib may also be offered in combination with fulvestrant in patients exposed to prior hormone therapy and up to one line of chemotherapy, on the basis of data from the phase III PALOMA-3 trial. PFS was improved compared with fulvestrant alone; OS data are immature (Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: intermediate).

Qualifying statements. Palbociclib should be administered once per day for 21 days every 28 days. The primary toxicity is neutropenia; blood counts should be monitored on day 14 of the first two cycles and at the start of each 28-day cycle, with neutropenia managed with dose delays and reductions.

Approval is for letrozole and palbociclib; any AI could be substituted, depending on individual tolerance, although no data exist at present. On the basis of current data, palbociclib can be used in the first-line setting in patients whose disease retains sensitivity to AIs or in the later-line setting in combination with fulvestrant.

Literature review and analysis. CDK 4/6 inhibitors were shown to be active in HR-positive and HER2-positive cell lines,[7] leading to a randomized phase II trial comparing letrozole with letrozole plus the CDK 4/6 inhibitor palbociclib as first-line treatment of HR-positive MBC.[7] The addition of palbociclib doubled PFS, without having an impact on OS; treatment was well tolerated, with the primary toxicity being uncomplicated neutropenia. Palbociclib was administered by mouth for 21 days every 28 days. A similar trial design was used in the randomized phase III PALOMA-2 trial; data are expected in 2016 (Data Supplement 8).

The PALOMA-3 trial randomly assigned patients with prior exposure to AIs (including premenopausal women undergoing ovarian suppression) to palbociclib or placebo in combination with fulvestrant and demonstrated more than a doubling in PFS with the addition of palbociclib.[17] Survival analysis is immature. Toxicities included a significant and marked increase in grade 3 to 4 neutropenia.

Two other CDK 4/6 inhibitors (ribociclib and abemaciclib) are being tested in phase II and III trials in combination with hormonal agents. Ribociclib is being administered for 21 days every 28 days and is also associated with neutropenia. Abemaciclib is being administered continuously; diarrhea is occurring more frequently than neutropenia.[75]

Clinical interpretation. Palbociclib in combination with letrozole received accelerated FDA approval as first-line therapy for HR-positive MBC, with final approval pending the results of the phase III trial of the same design. This treatment can now be considered as a treatment option for patients in this setting.

Although there are no data supporting other AIs in combination with palbociclib, it is reasonable to consider other nonsteroidal or steroidal AIs in the first-line setting on the basis of individual tolerance. On the basis of the data from PALOMA-3, it is also reasonable to consider the combination of fulvestrant and palbociclib in patients experiencing progression with AIs and with no prior exposure to CDK inhibitors. Blood counts must be monitored before the start of each new cycle as well as on day 14 of the first two cycles, with dose delays and reductions to manage neutropenia. Phase III data on ribociclib and abemaciclib, as well as data on palbociclib in the first-line setting, will be available in the near future.

CLINICAL QUESTION 4

Does estrogen or progesterone expression (high *v* low expression) affect hormone therapy considerations and modify recommendations for hormone therapy—either the recommended agents or dosing details—among pre-, peri-, and postmenopausal women?

Recommendation 4

Hormone therapy should be offered to patients whose tumors express any level of ER and/or progesterone receptor (PR) (Type: evidence and consensus based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statements. Although in general higher levels of ER and PR expression suggest greater likelihood of benefit from endocrine therapy for metastatic disease, there are no specific thresholds beyond positivity for recommending treatment. Relative expression levels vary significantly depending on technique and possibly tumor location. Testing for receptors should be performed on metastatic tumor tissue to confirm HR expression and HER2 status whenever feasible and clinically indicated, because data suggest that there is potential for change in receptor status from early- to late-stage tumors.

Literature review and analysis. There are no current data to inform this question.[76-78]

Clinical interpretation. At the present time, given the appropriate clinical situation, hormone therapy should be considered for patients whose tumors express ER and/or PR. Although in general higher levels of ER and PR expression suggest greater likelihood of benefit from endocrine therapy for metastatic disease, there are no specific thresholds beyond positivity for recommending treatment. Relative expression levels vary significantly depending on technique and possibly tumor location. Testing for receptors should be performed routinely on metastatic tumor tissue to confirm HR expression, because a number of data sets have demonstrated discordance between receptor status from early- to late-stage disease. Testing should include not only ER and PR but also HER2. Please refer to the ASCO recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer Clinical Practice Guideline Update[78a] for guidance on HER2 testing. There may be special settings in which a biopsy is not feasible; in such settings, a biopsy should be considered in the future if disease status or location changes. Caution should be used in interpreting receptor results obtained from bone biopsies because processing may affect results.

CLINICAL QUESTION 5

How does adjuvant treatment affect recommendations for treatment in the metastatic or advanced setting?

Recommendation 5

Treatment recommendations should be offered on the basis of type of adjuvant treatment, disease-free interval, and extent of disease at the time of recurrence (Figs 1 and 2). A specific hormonal agent may be used again if recurrence occurs > 12 months from last treatment (Type: evidence and consensus based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statement. Recurrence after short exposure to adjuvant hormone therapy suggests relative hormone resistance. Recurrence on or within 12 months of last exposure to a specific hormonal agent is evidence for resistance to that agent; an alternate hormone therapy should be considered using the sequential treatment approach.

Literature review and analysis. Adjuvant hormone therapy is almost universally prescribed for patients with early-stage, HR-positive breast cancer, and current data suggest that longer-duration therapy will result in improved disease-free survival. A majority of postmenopausal women will receive at least 5 years of an AI. Premenopausal women have usually been treated with tamoxifen with or without ovarian suppression, although AIs combined with ovarian suppression may be increasingly used on the basis of recent data. The type of hormone therapy administered and the time from last treatment to recurrence are critical parameters in determining treatment in the metastatic setting. Clinical trials have considered relapse during or within 12 months of adjuvant hormone therapy as evidence for resistance to that therapy. In this situation, recommendations for second-line hormone therapy should be followed. For patients whose disease is resistant to adjuvant tamoxifen, nonsteroidal AIs should be considered. Duration of adjuvant hormone therapy before the diagnosis of recurrence is also important. Chemotherapy should be considered for patients with rapid recurrence of visceral dominant or life-threatening disease within 1 to 2 years of starting adjuvant hormone therapy, because this is evidence of resistance to hormone therapy.

Clinical interpretation. Recommendations are on the basis of prior treatment, disease-free interval, and extent of disease at the time of recurrence (Table 2).

CLINICAL QUESTION 6

In which patients or settings is hormone therapy recommended over chemotherapy?

6.1 Is there a role for combined cytotoxic and endocrine therapies?
6.2 What is the optimal duration of treatment with hormone therapy?

Recommendation 6

Endocrine therapy should be recommended as initial treatment for patients with HR-positive MBC, except for patients with immediately life-threatening disease or for those who experience rapid visceral recurrence during adjuvant endocrine therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Qualifying statement. Other than in the setting of immediately life-threatening disease, there is no evidence that starting with chemotherapy improves any outcome measure, including OS, toxicity, and QoL.

Literature review and analysis. A Cochrane analysis evaluated randomized trials comparing chemotherapy with endocrine therapy in patients with MBC.[8] In six randomized trials including 692 women, there was no significant difference in OS. In a pooled analysis of eight trials, chemotherapy was associated with an increase in objective response rate, although this result was found to be associated with significant heterogeneity. Of seven published trials, six found increased toxicity with chemotherapy. One trial evaluated QoL and concluded that it was better with chemotherapy. The analysis concluded that endocrine therapy should be used before chemotherapy except in patients with rapidly progressive disease.

Clinical interpretation. Endocrine therapy is the preferred initial treatment for patients with HR-positive MBC, except for patients with immediately life-threatening disease or for those who experience rapid visceral recurrence during adjuvant endocrine therapy. There is no evidence that starting with chemotherapy improves any outcome measure, including OS, toxicity, and QoL. Additional research in encouraged in this area, with current treatment and diagnostic standards.

Question 6.1

Is there a role for combined cytotoxic and endocrine therapies?

Recommendation 6.1

The use of combined endocrine therapy and chemotherapy is not recommended (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Question 6.2

What is the optimal duration of treatment with hormone therapy?

Recommendation 6.2

Treatment should be administered 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 (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statements. Assessment of progression may be challenging because of the combination of difficulty in interpreting imaging and the indolent nature of HR-positive disease in some patients. Treatment should focus on patient outcomes and symptoms. Tumor flare reactions (increase in tumor-related symptoms) can occur, particularly with tamoxifen and estradiol; were observed shortly after beginning a new endocrine treatment; and can be confused with disease progression. Treatment-related toxicity may be a reason to change therapy. Patient outcomes were not improved by changing therapy based solely on tumor markers or circulating tumor cells.

CLINICAL QUESTION 7

Is there a role for additional biomarkers in the selection of treatment for patients for HR-positive disease?

7.1 What is the role of genomic profiling or intrinsic subtypes in this population?

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 HR-positive MBC (Type: consensus based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Qualifying statements. There is no evidence to date demonstrating a role for specific biomarkers other than ER, PR, and HER2. Useful biomarkers would allow additional selection of specific effective therapy.

Literature review and analysis. There is no evidence as yet demonstrating a role for specific biomarkers other than ER, PR, and HER2. Useful biomarkers would allow additional selection of specific effective therapy.

Clinical interpretation. 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 HR-positive MBC.

Question 7.1

What is the role of genomic profiling or intrinsic subtypes in this population?

Recommendation 7.1

Genomic or expression profiling should not be used to select treatment for HR-positive MBC (Type: consensus based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Qualifying statement. Intrinsic subtypes have been associated with prognosis but have not yet been shown to aid in the selection of effective treatment. HR-positive tumors associated with mutations in the *BRCA1* and *BRCA2* genes seem to have a response to hormone therapy similar to that of sporadic cancers.

Literature review and analysis. Intrinsic subtypes on the basis of gene expression have been associated with prognosis but have not yet been shown to aid in the selection of effective treatment.[79,80] Genomic profiling to identify specific mutations for potential targeting is of increasing interest. However, there are no prospective data to demonstrate that selection of specific treatments on the basis of genomic profiling results in better disease outcomes. HR-positive tumors associated with mutations in the *BRCA1* and *BRCA2* genes seem to have a response to hormone therapy similar to that of sporadic cancers.

Clinical interpretation. There is no routine clinical role for genomic or expression profiling in the selection of treatment for HR-positive MBC.

CLINICAL QUESTION 8

How does HER2 positivity affect treatment of patients with HR-positive MBC?

Recommendation 8

The addition of HER2-targeted therapy to first-line AIs should be offered to patients with HR-positive, HER2-positive MBC in whom chemotherapy is not immediately indicated. The addition of HER2-targeted therapy to first-line AIs improved PFS, without a demonstrated improvement in OS. HER2-targeted therapy combined with chemotherapy resulted in improvements in OS and is the preferred first-line approach in most cases (Type: evidence and consensus based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statements. The choice of chemotherapy versus hormone therapy should be driven by the clinical and biologic characteristics of the disease, with hormone therapy reserved for more indolent disease. Chemotherapy in combination with HER2-targeted therapy is indicated in de novo and visceral dominant disease, because this treatment offers a survival benefit compared with chemotherapy alone. Hormone therapy has also been used as maintenance treatment after response to chemotherapy, combined with ongoing HER2-targeted therapy, although there is no evidence to support benefit in this setting.

Literature review and analysis. Expression of the HER2/neu receptor or *HER2* gene amplification has been associated with reduced and shorter duration of response to endocrine therapy because of cross talk with the ER and activated growth factor receptor signaling pathways.[81] Two randomized trials evaluated the addition of HER2-targeted agents to first-line AI therapy in MBC. The first study evaluated trastuzumab plus anastrozole versus anastrozole alone in patients with HR-positive, HER2-positive disease, and the second study evaluated letrozole plus lapatinib versus letrozole alone in patients with HR-positive disease and also evaluated the subset who were HER2 positive.[5,6] Both trials reported a significant improvement in PFS, although the difference was larger in the lapatinib study. Of note, PFS in both trials was short for patients treated with an AI alone, ranging from 2.4 to 3 months. Neither study showed a difference in OS; treatment was well tolerated. A small randomized trial reported a large but nonsignificant difference in TTP favoring letrozole plus trastuzumab over letrozole.[41] There are no data evaluating the efficacy of tamoxifen plus trastuzumab, although this combination could be considered in patients experiencing disease progression with AIs who are not candidates for chemotherapy combined with HER2-targeted therapy.

Clinical interpretation. In patients with HR-positive, HER2-positive MBC, the addition of HER2-targeted therapy to first-line AIs improved PFS, without a demonstrated improvement in OS. HER2-targeted therapy combined with chemotherapy resulted in improvements in OS; therefore, in most cases, this is the preferred first-line approach.

The choice of chemotherapy versus hormone therapy should be driven by the clinical and biologic characteristics of the disease, with hormone therapy reserved for more indolent disease. Hormone therapy has also been used as maintenance treatment after response to chemotherapy, combined with ongoing HER2-targeted therapy, although there is no evidence to support benefit in this setting. For ASCO guidance on treatment for patients with advanced HER2-positive breast cancer, please see the Clinical Practice Guideline on systemic therapy for patients with advanced HER2-positive breast cancer.[80a]

CLINICAL QUESTION 9

What are the future directions for treatment in this patient population?

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 hormone therapy in metastatic disease (Type: evidence and consensus based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Qualifying statements. Determining biomarkers to predict response to specific targeted agents is a critical investigative path. Ongoing clinical trials are investigating mechanisms of resistance, predictive biomarkers, and a series of novel agents added to hormone therapy for MBC, with some of the most promising agents including PI3K inhibitors, additional CDK 4/6 inhibitors, HDAC, androgen receptor antagonists, selective ER downregulators such as fulvestrant, and new HER2-targeted agents. In addition, biomarker studies evaluating ER mutations and their impact on treatment outcomes and drug selection are under way.[82]

Two trials have now been reported comparing the combination of a pan-PI3K inhibitor and hormone therapy. Both trials showed no or minimal improvements in PFS and a significant increase in toxicity with the addition of the PI3K inhibitor.[51,52] Additional trials are ongoing with alpha-specific PI3K inhibitors (Data Supplement 8).

Although the addition of bevacizumab to first-line endocrine therapy modestly improved PFS in two trials, OS was not improved, and toxicity was increased.[48,49] This therapy is not recommended in combination with hormone therapy for breast cancer.

Literature review and analysis. Preclinical research has identified pathways important in hormone resistance. The PI3K pathway is the most common altered pathway in HR-positive disease. It has been challenging to identify biomarkers that predict response to specific agents or combinations, other than ER and PR. Biomarkers identified in clinical trials have been prognostic but not predictive.

The phase II FERGI trial randomly assigned 168 women with HR-positive MBC with prior exposure to an AI to receive the pan-PI3K inhibitor pictilisib (GDC-0941) or placebo in combination with fulvestrant.[51] There was no significant difference in PFS between the two arms, and toxicities including rash and diarrhea resulted in dose modifications and discontinuations. There was no difference in efficacy on the basis of *PI3K* mutation status. The phase III BELLE-2 trial randomly assigned 1,147 postmenopausal women with HR-positive MBC experiencing progression during or after an AI to receive the pan-PI3K inhibitor buparlisib or placebo with fulvestrant.[52] PFS was improved from 5 to 6.9 months, which was statistically but not clinically significant in either the whole group or in patients whose tumors had activated PI3K. Toxicities included grade 3 to 4 liver function abnormalities, hyperglycemia, rash, fatigue, and depression. An exploratory analysis in a small subset found higher response rates in those receiving buparlisib who had evidence of *PIK3CA* mutations in circulating tumor DNA. On the basis of these data, pan-PI3K inhibitors are unlikely to move forward in the clinical setting. However, it is clear that additional studies should include analyses of pathway activation, and evaluation of circulating tumor DNA is a promising area for further study.

Alpha-specific PI3K inhibitors have demonstrated efficacy in the treatment of HR-positive but hormone-resistant disease without clear association with underlying *PI3K* mutation status. Several ongoing clinical trials are evaluating these agents in the MBC setting, including the SOLAR-1 trial (alpelisib) and the SANDPIPER trial (Data Supplement 8).

HDAC inhibitors can block post-translational silencing of the ER. The HDAC inhibitor entinostat improved PFS and OS when combined with exemestane compared with exemestane alone in a randomized phase II trial.[50] A phase III trial (ClinicalTrials.gov identifier NCT02115282) is ongoing (Data Supplement 8).

Inhibitors of the fibroblast growth factor receptor have demonstrated activity in the treatment of HR-positive MBC. Two agents (lucitinib and dovitinib) are being actively studied in phase II clinical trials.[83]

A majority of HR-positive tumors also express the androgen receptor. Recent studies have suggested that antagonists of the androgen receptor may have activity in hormone-resistant HR-positive MBC, and additional trials are planned or ongoing.

A study of the addition of pertuzumab in combination with trastuzumab and an AI is being compared with trastuzumab plus an AI in an ongoing randomized trial (ClinicalTrials.gov identifier NCT01491737), with the goal of both assessing the benefit of pertuzumab and identifying patients whose HER2-positive tumors can be treated with hormone therapy rather than chemotherapy in the first-line setting (Data Supplement 8).

Combinations of targeted therapies have demonstrated efficacy in preclinical studies. Several of these combinations have been or are being testing in clinical trials, including the combination of CDK 4/6 and PI3K inhibition.[84] Toxicity from combination therapy is a significant issue that limits at least some approaches. The combination of an mTOR inhibitor and an inhibitor of IGFR did not improve outcomes relative to the mTOR inhibitor alone in one recent phase II trial.

Mutations in the ER (*ESR1*) have been identified as markers of resistance and poor outcomes, although no specific therapy to target this site has been identified to date.

Clinical interpretation. Multiple clinical trials are ongoing or planned, with a focus on improving response to hormone therapy in metastatic and early-stage disease. Biomarkers to predict response to specific targeted agents is a critical investigative path. Areas of specific interest in combination with hormone therapy include PI3K inhibitors, HDAC inhibitors, CDK 4/6 inhibitors, fibroblast growth factor receptor inhibitors, selective ER downregulators, combinations of HER2-targeted therapies, and combinations of different targeted therapies.

Enrollment in clinical trials should be encouraged at all lines of therapy and in all stages of treatment. Physician and patient education about clinical trials is crucial. Future studies should strive to include at least a population of patients with multiple chronic conditions (MCCs) to better represent the real-world population.

DISCUSSION

Endocrine therapy is a mainstay of treatment for women with HR-positive MBC. High-level evidence exists for use of most of the commonly prescribed treatments, and a vast historical literature is available to guide overarching treatment principles. Most women with HR-positive MBC will be candidates for multiple lines of endocrine therapy and for multiple lines of chemotherapy when their tumors are resistant to hormonal agents. It is not uncommon for patients to alternate between endocrine therapy and chemotherapy over the course of their treatment program, on the basis of the extent of cancer burden, the adverse effects of therapy, and the symptoms associated with their cancer.

As shown in the algorithms (Figs 1 and 2), a variety of sequences for endocrine therapy can be appropriate. The choice of a specific agent or approach is influenced by menopausal status, prior adjuvant endocrine therapy, disease-free interval, prior treatment of advanced disease, and the adverse effect profile of the treatment plan. Because few of these treatment nodes are associated with marked survival advantages or major differences in clinical benefit, clinicians and patients can exercise discretion in choosing appropriate treatments. For postmenopausal patients, the panel prefers single-agent AI therapy, or AI in combination with fulvestrant for select situations, as initial therapy.

The CDK 4/6 inhibitor palbociclib may be added to first-line therapy with an AI. In second-line treatment for postmenopausal women, the panel recommends either fulvestrant plus palbociclib or exemestane plus everolimus; single-agent hormone therapy can also be considered. The panel prefers the combination of tamoxifen or an AI with ovarian suppression as initial therapy for premenopausal patients. Treatment thereafter mirrors that recommended for postmenopausal women, with ongoing ovarian suppression and use of an AI as second-line therapy if tamoxifen was used in the first line, with consideration of subsequent agents, including targeted agents, as appropriate.

Clinicians are reminded that endocrine therapy may be reintroduced after the initiation of chemotherapy as either maintenance therapy or as a next step in sequential treatment. Although these strategies are not frequently studied in clinical trials evaluating endocrine agents for regulatory purposes, it is an appropriate and important consideration for clinical practice. Clinicians can offer endocrine treatment as maintenance therapy after a successful response

to chemotherapy (or in the case of HR-positive, HER2-positive tumors, after a response to chemotherapy and anti-HER2 agents, with continuation of the anti-HER2 agents) or as treatment of chemotherapy-resistant disease. Considerations in the choice of agent when endocrine therapy is reintroduced are similar to those outlined in this article. Anecdotal reports have described tumor response or prolonged periods of stable disease with reintroduction of endocrine therapy using either new or previously administered agents.

Agents targeted to biologic pathways associated with resistance to hormone therapy are being studied in numerous clinical trials, with encouraging preliminary data. Phase III trials testing CDK 4/6, PI3K, and HDAC inhibitors are ongoing or have completed accrual, with results expected in 2015 to 2016. These new approaches, although costly, may change our approach to the treatment of HR-positive MBC in the near future.

EXTERNAL REVIEW

The draft clinical practice guideline was distributed to three clinicians who were not members of the Expert Panel for review (Acknowledgment [online-only]). Although the three reviewers were in agreement with the systematic review results, the Expert Panel's interpretation of the evidence, and the draft recommendations, comments were received concerning the lack of guidance around rebiopsying metastatic tissue and retesting of ER and HER2. In response, the working group added a section covering these to the Introduction. All other comments, both substantive and editorial, were considered by the working group, and changes were made to address all comments as warranted.

RECOMMENDATIONS

The recommendations were developed by a multidisciplinary group of experts using evidence from systematic reviews with meta-analyses and randomized trials (phases II and III), along with clinical experience. Ratings for the type of recommendation and strength of the evidence are offered (rating definitions are provided in the Methodology Supplement).

SPECIAL COMMENTARY

The treatment of HR-positive MBC is rapidly changing, with new targeted therapies now available in combination with hormonal agents. Results from a number of phase II and III trials will be reported in the next 2 years; this is likely to further affect the recommendations set forth in this guideline.

PATIENT AND CLINICIAN COMMUNICATION

This section is on the basis of patient and clinician experience and selected literature but was not part of the systematic review of the literature. Although there are differences between issues facing patients with different types of metastatic solid tumors, clinicians are encouraged to refer to a similar discussion in the ASCO Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer (2009)[85] and to literature on risk communication for patients with cancer.[86] A patient who is newly diagnosed with metastatic disease versus one for whom first- or second-line treatment or greater 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. When communicating, clinicians should consider issues relevant to patients with MBC, including the importance of evidence-based treatment, referral to http://www.cancer.net links, psychosocial support, and introduction of the concepts of concurrent palliative and antitumor therapy.[85,87-89]

Research that focuses on discussing specific issues with patients with advanced breast cancer is still needed. Teams should be prepared to present the information in this guideline in a format tailored to the patient's and/or caregiver's learning style and to involve the patient as appropriate in decision making. Discussions with patients should include key subjects. Suggested sample talking points are provided in Data Supplement 4.

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. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who belong to racial or ethnic minorities disproportionately suffer from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving poor-quality care than other Americans.[90-94] Many other patients lack access to care because of their geography or 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.

MCCs

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as MCCs—is challenging. Patients with MCCs are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials, the study selection criteria of which may exclude these patients to avoid potential interaction effects or confounding of results associated with MCCs. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups in making recommendations for care in this heterogeneous patient population.

Because many patients for whom guideline recommendations apply present with MCCs, any management plan needs to take into account the complexity and uncertainty created by the presence of MCCs and highlight 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 plans.

Taking these considerations into account, practice guidelines should provide information on how to apply the recommendations for patients with MCCs, perhaps as a qualifying statement for recommended care. 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 MCCs.

For female patients with breast cancer who are younger than 65 years of age, the 10 most common comorbid conditions are hypertension, hyperlipidemia, depression, arthritis, anemia, diabetes, ischemic heart disease, chronic obstructive pulmonary disease, chronic kidney disease, and heart failure. For female patients with breast cancer who are older than 65 years of age, the 10 most common comorbid conditions are hypertension, hyperlipidemia, arthritis, anemia, ischemic heart disease, diabetes, cataracts, heart failure, depression, and chronic kidney disease. The table in Data Supplement 5 lists details on the number of patients affected by these comorbid conditions and supplementary information. Estimating a patient's survival with MCCs exclusive of MBC can be easily done in an office setting and may be helpful in selecting care (http://eprognosis.ucsf.edu).

COST IMPLICATIONS

The guideline panel understands that the treatment of metastatic cancer is complicated by the cost of treatment and that this may limit options in some situations. The use of combination hormone therapy, particularly with targeted agents, clearly adds both the cost of acquiring the agents as well as the cost of managing adverse effects. This guideline outlines the optimal treatment approach without considering cost or availability in specific geographic areas of the world. Recommendations are on the basis of clinical trials, and limitations of existing data are outlined. This information should help with decision making when the cost of therapy limits access to specific treatments.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and cancer survivors and also to provide adequate services in the face of limited resources. The guideline Bottom Line was designed to facilitate implementation of recommendations. This guideline will be distributed widely throughout the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*. Treatments that control symptoms, delay the onset of chemotherapy, and delay progression of disease should be emphasized within the contexts of cost and toxicity.

LIMITATIONS 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. It is critical that appropriate PRO measures to evaluate symptoms and adverse effects be included in these studies. Information regarding patient perspectives about risks and benefits of novels therapies is necessary to inform patient and physician decision making and should include perceptions about interventions used to ameliorate toxicity. 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 on the basis of biologic subsets of disease and the sequential or combination use of ovarian suppression and hormone therapy in premenopausal women. Future directions include understanding the possible benefits of combining the current approved dose of fulvestrant (500 mg every 2 weeks for three cycles, then 500 mg per month) with AIs as first-line therapy for MBC and studying combinations of agents targeted to biologic pathways with hormone therapy. 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. The long-term goal of these trials is to move more effective treatment approaches to the early-stage setting. One major goal is to identify markers or signatures that predict response to specific therapies. To date, these studies have only confirmed prognostic markers that do not predict benefit from specific therapies. Collaboration among groups and analyses of pathway activation are important steps toward identifying predictive markers. Future studies should strive to include at least a population of patients with MCCs to better represent the real-world population likely to use a specific new therapy.

ADDITIONAL RESOURCES

Additional information, including Data Supplements, evidence tables, and clinical tools and resources, can be found at http://www.asco.org/guidelines/advancedendocrinebreast. Patient information is available there and at http://www.cancer.net.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
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REFERENCES

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2015. CA Cancer J Clin 65:5-29, 2015

2. Clarke CA, Keegan TH, Yang J, et al: Age-specific incidence of breast cancer subtypes: Understanding the black-white crossover. J Natl Cancer Inst 104:1094-1101, 2012

3. Lobbezoo DJ, van Kampen RJ, Voogd AC, et al: Prognosis of metastatic breast cancer subtypes: The hormone receptor/HER2-positive subtype is associated with the most favorable outcome. Breast Cancer Res Treat 141:507-514, 2013

4. Baselga J, Campone M, Piccart M, et al: Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 366:520-529, 2012

5. Johnston S, Pippen J Jr, Pivot X, et al: Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor–positive metastatic breast cancer. J Clin Oncol 27:5538-5546, 2009

6. Kaufman B, Mackey JR, Clemens MR, et al: Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2–positive, hormone receptor–positive metastatic breast cancer: Results from the randomized phase III TAnDEM study. J Clin Oncol 27:5529-5537, 2009

7. Finn RS, Crown JP, Lang I, et al: The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): A randomised phase 2 study. Lancet Oncol 16:25-35, 2015

8. Wilcken N, Hornbuckle J, Ghersi D: Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database Syst Rev 2:CD002747, 2003

9. Robertson JFR, Paridaens R, Bogaerts J, et al: Visceral metastases from hormone receptor positive breast cancer are as sensitive to endocrine therapy as non-visceral metastases. Cancer Res 75 , 2015 (abstr P1-13-02)

10. Sledge GW Jr, Hu P, Falkson G, et al: Comparison of chemotherapy with chemohormonal therapy as first-line therapy for metastatic, hormone-sensitive breast cancer: An Eastern Cooperative Oncology Group study. J Clin Oncol 18:262-266, 2000

11. Pritchard KI: Combining endocrine agents with chemotherapy: Which patients and what sequence? Cancer 112:718-722, 2008 (suppl)

11a. Partridge A, Rumble RB, Carey LA, et al: Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2–negative (or unknown) advanced breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 32:3307-3329, 2014

12. Mehta RS, Barlow WE, Albain KS, et al: Combination anastrozole and fulvestrant in metastatic breast cancer. N Engl J Med 367:435-444, 2012

13. Bergh J, Jönsson PE, Lidbrink EK, et al: FACT: An open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. J Clin Oncol 30:1919-1925, 2012

14. Robertson JF, Lindemann JP, Llombart-Cussac A, et al: Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: Follow-up analysis from the randomized 'FIRST' study. Breast Cancer Res Treat 136:503-511, 2012

15. Robertson JFR, Llombart-Cussac A, Feltl D, et al: Fulvestrant 500 mg versus anastrozole as first-line treatment for advanced breast cancer: Overall survival from the phase II 'FIRST' study. Cancer Res 75, 2015 (abstr S6-04)

16. Yardley DA, Noguchi S, Pritchard KI, et al: Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther 30: 870-884, 2013 (erratum: Adv Ther 31:1008-1009, 2014)

17. Turner NC, Ro J, André F, et al: Palbociclib in hormone-receptor-positive advanced breast cancer. N Engl J Med 373:209-219, 2015

18. Klijn JG, Beex LV, Mauriac L, et al: Combined treatment with buserelin and tamoxifen in premenopausal metastatic breast cancer: A randomized study. J Natl Cancer Inst 92:903-911, 2000

19. Klijn JG, Blamey RW, Boccardo F, et al: Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: A meta-analysis of four randomized trials. J Clin Oncol 19:343-353, 2001

20. Chia S, Gradishar W, Mauriac L, et al: Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor–positive, advanced breast cancer: Results from EFECT. J Clin Oncol 26:1664-1670, 2008

21. Di Leo A, Jerusalem G, Petruzelka L, et al: Final analysis of overall survival for the phase III CONFIRM trial: Fulvestrant 500 mg versus 250 mg. Cancer Res 72, 2012 (abstr S1-4)

22. Iwata H, Masuda N, Ohno S, et al: A randomized, double-blind, controlled study of exemestane versus anastrozole for the first-line treatment of postmenopausal Japanese women with hormone-receptor-positive advanced breast cancer. Breast Cancer Res Treat 139:441-451, 2013

23. Llombart-Cussac A, Ruiz A, Antón A, et al: Exemestane versus anastrozole as front-line endocrine therapy in postmenopausal patients with hormone receptor-positive, advanced breast cancer: Final results from the Spanish Breast Cancer Group 2001-03 phase 2 randomized trial. Cancer 118:241-247, 2012

24. Ohno S, Rai Y, Iwata H, et al: Three dose regimens of fulvestrant in postmenopausal Japanese women with advanced breast cancer: Results from a double-blind, phase II comparative study (FINDER1). Ann Oncol 21:2342-2347, 2010

25. Pritchard KI, Rolski J, Papai Z, et al: Results of a phase II study comparing three dosing regimens of fulvestrant in postmenopausal women with advanced breast cancer (FINDER2). Breast Cancer Res Treat 123:453-461, 2010

26. Xu B, Jiang Z, Shao Z, et al: Fulvestrant 250 mg versus anastrozole for Chinese patients with advanced breast cancer: Results of a multicentre, double-blind, randomised phase III trial. Cancer Chemother Pharmacol 67:223-230, 2011

27. Amir E, Clemons M, Purdie CA, et al: Tissue confirmation of disease recurrence in breast cancer patients: Pooled analysis of multi-centre, multidisciplinary prospective studies. Cancer Treat Rev 38:708-714, 2012

28. Amir E, Miller N, Geddie W, et al: Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. J Clin Oncol 30:587-592, 2012

29. Pusztai L, Viale G, Kelly CM, et al: Estrogen and HER-2 receptor discordance between primary breast cancer and metastasis. Oncologist 15:1164-1168, 2010

30. Chi F, Wu R, Zeng Y, et al: Effects of toremifene versus tamoxifen on breast cancer patients: A meta-analysis. Breast Cancer 20:111-122, 2013

31. Cope S, Ouwens MJ, Jansen JP, et al: Progression-free survival with fulvestrant 500 mg and alternative endocrine therapies as second-line treatment for advanced breast cancer: A network meta-analysis with parametric survival models. Value Health 16:403-417, 2013

32. Xu HB, Liu YJ, Li L: Aromatase inhibitor versus tamoxifen in postmenopausal woman with advanced breast cancer: A literature-based meta-analysis. Clin Breast Cancer 11:246-251, 2011

33. Tan PS, Haaland B, Montero AJ, et al: Anastrozole in combination with fulvestrant in the first line treatment of hormone receptor positive advanced breast cancer: A meta-analysis. J Clin Oncol 31, 2013 (suppl; abstr e11591)

34. Valachis A, Mauri D, Polyzos NP, et al: Fulvestrant in the treatment of advanced breast cancer: A systematic review and meta-analysis of randomized controlled trials. Crit Rev Oncol Hematol 73: 220-227, 2010

35. Bachelot TD, Jerusalem GHM, Cikalo M, et al: Comparative efficacy of everolimus versus fulvestrant for hormone-receptor-positive (HR+) advanced breast cancer (ABC) following progression/recurrence after first-line treatment: A network meta-analysis. J Clin Oncol 31, 2013 (suppl; abstr e11602)

36. Di Leo A, Jerusalem G, Petruzelka L, et al: Final overall survival: Fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. J Natl Cancer Inst 106:djt337, 2014

37. Paridaens RJ, Dirix LY, Beex LV, et al: Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: The European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. J Clin Oncol 26:4883-4890, 2008

38. Johnston SR, Kilburn LS, Ellis P, et al: Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): A composite, multicentre, phase 3 randomised trial. Lancet Oncol 14:989-998, 2013

39. Johnston SRD, Basik M, Hegg R, et al: Phase II randomized study of the EGFR, HER2, HER3 signaling inhibitor AZD8931 in combination with anastrozole (A) in women with endocrine therapy (ET) naive advanced breast cancer (MINT). J Clin Oncol 31, 2013 (suppl; abstr 531)

40. Burstein HJ, Cirrincione CT, Barry WT, et al: Endocrine therapy with or without inhibition of epidermal growth factor and human epidermal growth factor receptor 2: A randomized, double-blind, placebo-controlled phase III trial of fulvestrant with or without lapatinib for postmenopausal women with hormone receptor–positive advanced breast cancer—CALGB 40302 (Alliance). J Clin Oncol 32:3959-3966, 2014

41. Huober J, Fasching PA, Barsoum M, et al: Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer: Results of the eLEcTRA trial. Breast 21:27-33, 2012

42. Schwartzberg LS, Franco SX, Florance A, et al: Lapatinib plus letrozole as first-line therapy for HER-2+ hormone receptor-positive metastatic breast cancer.

Oncologist 15:122-129, 2010 (Erratum: Oncologist 15:327, 2010)

43. Bachelot T, Bourgier C, Cropet C, et al: Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer with prior exposure to aromatase inhibitors: A GINECO study. J Clin Oncol 30:2718-2724, 2012

44. Wolff AC, Lazar AA, Bondarenko I, et al: Randomized phase III placebo-controlled trial of letrozole plus oral temsirolimus as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer. J Clin Oncol 31:195-202, 2013

45. Piccart M, Hortobagyi GN, Campone M, et al: Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: Overall survival results from BOLERO-2. Ann Oncol 25:2357-2362, 2014

46. Clemons MJ, Cochrane B, Califaretti N, et al: Randomized phase II placebo-controlled trial of fulvestrant plus vandetanib in postmenopausal women with bone only or bone predominant, hormone receptor-positive metastatic breast cancer (MBC): OCOG Zamboney study—NCT00811369. J Clin Oncol 31, 2013 (suppl; abstr 574)

47. Robertson JF, Ferrero J-M, Bourgeois H, et al: Ganitumab with either exemestane or fulvestrant for postmenopausal women with advanced, hormone-receptor-positive breast cancer: A randomised, controlled, double-blind, phase 2 trial. Lancet Oncol 14: 228-235, 2013

48. Martín M, Loibl S, von Minckwitz G, et al: Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer: The letrozole/fulvestrant and avastin (LEA) study. J Clin Oncol 33:1045-1052, 2015

49. Dickler MN, Barry WT, Cirrincione CT, et al: Phase III trial evaluating the addition of bevacizumab to letrozole as first-line endocrine therapy for treatment of hormone-receptor positive advanced breast cancer: CALGB 40503 (Alliance). J Clin Oncol 33, 2015 (suppl; abstr 501)

50. Yardley DA, Ismail-Khan RR, Melichar B, et al: Randomized phase II, double-blind, placebo-controlled study of exemestane with or without entinostat in postmenopausal women with locally recurrent or metastatic estrogen receptor-positive breast cancer progressing on treatment with a nonsteroidal aromatase inhibitor. J Clin Oncol 31:2128-2135, 2013

51. Krop I, Johnston S, Mayer IA, et al: The FERGI phase II study of the PI3K inhibitor pictilisib (GDC-0941) plus fulvestrant vs fulvestrant plus placebo in patients with ER+, aromatase inhibitor (AI)-resistant advanced or metastatic breast cancer: Part I results. Cancer Res 75, 2015 (abstr S2-02)

52. Baselga J, Im SA, Iwata H, et al: PIK3CA status in circulating tumor DNA (ctDNA) predicts efficacy of buparlisib (BUP) plus fulvestrant (FULV) in postmenopausal women with endocrine-resistant HR+/HER2– advanced breast cancer (BC): First results from the randomized, phase III BELLE-2 trial. Presented at the San Antonio Breast Cancer Symposium, San Antonio, TX, December 8-12, 2015

53. Di Leo A, Jerusalem G, Petruzelka L, et al: Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. J Clin Oncol 28: 4594-4600, 2010

54. Rugo HS, Pritchard KI, Gnant M, et al: Incidence and time course of everolimus-related adverse events in postmenopausal women with hormone receptor-positive advanced breast cancer: Insights from BOLERO-2. Ann Oncol 25: 808-815, 2014

55. Rugo HS: Dosing and safety implications for oncologists when administering everolimus to patients with hormone receptor-positive breast cancer. Clin Breast Cancer 16:18-22, 2016

56. Yardley DA, Hortobagyi GN, Lebrun F, et al: Patient-reported physical, emotional, and social functioning in advanced breast cancer: Insights from BOLERO-2. J Clin Oncol 31, 2013 (suppl; abstr 553)

57. Bonneterre J, Thürlimann B, Robertson JF, et al: Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: Results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol 18:3748-3757, 2000

58. Mouridsen H, Gershanovich M, Sun Y, et al: Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: Results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol 19:2596-2606, 2001

59. Nabholtz JM, Buzdar A, Pollak M, et al: Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: Results of a North American multicenter randomized trial. J Clin Oncol 18:3758-3767, 2000

60. Suman VJ, Ellis MJ, Ma CX: The ALTERNATE trial: Assessing a biomarker driven strategy for the treatment of post-menopausal women with ER+/Her2-invasive breast cancer. Chin Clin Oncol 4:34, 2015

61. Taylor CW, Green S, Dalton WS, et al: Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: An intergroup study. J Clin Oncol 16:994-999, 1998

62. Ingle JN, Krook JE, Green SJ, et al: Randomized trial of bilateral oophorectomy versus tamoxifen in premenopausal women with metastatic breast cancer. J Clin Oncol 4:178-185, 1986

63. Crump M, Sawka CA, DeBoer G, et al: An individual patient-based meta-analysis of tamoxifen versus ovarian ablation as first line endocrine therapy for premenopausal women with metastatic breast cancer. Breast Cancer Res Treat 44:201-210, 1997

64. Carlson RW, Theriault R, Schurman CM, et al: Phase II trial of anastrozole plus goserelin in the treatment of hormone receptor–positive, metastatic carcinoma of the breast in premenopausal women. J Clin Oncol 28:3917-3921, 2010

65. Cheung KL, Agrawal A, Folkerd E, et al: Suppression of ovarian function in combination with an aromatase inhibitor as treatment for advanced breast cancer in pre-menopausal women. Eur J Cancer 46: 2936-2942, 2010

66. Nishimura R, Anan K, Yamamoto Y, et al: Efficacy of goserelin plus anastrozole in premenopausal women with advanced or recurrent breast cancer refractory to an LH-RH analogue with tamoxifen: Results of the JMTO BC08-01 phase II trial. Oncol Rep 29:1707-1713, 2013

67. Gnant M, Pfeiler G, Stöger H, et al: The predictive impact of body mass index on the efficacy of extended adjuvant endocrine treatment with anastrozole in postmenopausal patients with breast cancer: An analysis of the randomised ABCSG-6a trial. Br J Cancer 109:589-596, 2013

68. Goodwin PJ: Obesity, insulin resistance and breast cancer outcomes. Breast 24:S56-S59, 2015 (suppl 2)

69. Gibson L, Lawrence D, Dawson C, et al: Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database Syst Rev 4:CD003370, 2009

70. Abrams J, Aisner J, Cirrincione C, et al: Dose-response trial of megestrol acetate in advanced breast cancer: Cancer and Leukemia Group B phase III study 8741. J Clin Oncol 17:64-73, 1999

71. Ellis MJ, Gao F, Dehdashti F, et al: Lower-dose vs high-dose oral estradiol therapy of hormone receptor–positive, aromatase inhibitor–resistant advanced breast cancer: A phase 2 randomized study. JAMA 302:774-780, 2009

72. Howell A, Dodwell DJ, Anderson H, et al: Response after withdrawal of tamoxifen and progestogens in advanced breast cancer. Ann Oncol 3: 611-617, 1992

73. Van Poznak C, Somerfield MR, Bast RC, et al: Use of biomarkers to guide decisions on systemic therapy for women with metastatic breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 33:2695-2704, 2015

74. Aapro M, Andre F, Blackwell K, et al: Adverse event management in patients with advanced cancer receiving oral everolimus: Focus on breast cancer. Ann Oncol 25:763-773, 2014

74a. Pfizer: www.pfizer.com/news/press-release/press-release-detail/pfizer_announces_positive_top_line_results_for_phase_3_paloma_2_clinical_trial_of_ibrance_palbociclib

75. Vidula N, Rugo HS: Cyclin-dependent kinase 4/6 inhibitors for the treatment of breast cancer: A review of preclinical and clinical data. Clin Breast Cancer 16:8-17, 2016

76. Reisenbichler ES, Lester SC, Richardson AL, et al: Interobserver concordance in implementing the 2010 ASCO/CAP recommendations for reporting ER in breast carcinomas: A demonstration of the difficulties of consistently reporting low levels of ER expression by manual quantification. Am J Clin Pathol 140:487-494, 2013

77. Thompson AM, Jordan LB, Quinlan P, et al: Prospective comparison of switches in biomarker status between primary and recurrent breast cancer: The Breast Recurrence In Tissues Study (BRITS). Breast Cancer Res 12:R92, 2010

78. Yamashita H, Yando Y, Nishio M, et al: Immunohistochemical evaluation of hormone receptor status for predicting response to endocrine therapy in metastatic breast cancer. Breast Cancer 13:74-83, 2006

78a. Wolff AC, Hammond MEH, Hicks DG, et al: Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 31:3997-4013, 2013

79. Cheang MC, Martin M, Nielsen TO, et al: Defining breast cancer intrinsic subtypes by quantitative receptor expression. Oncologist 20:474-482, 2015

80. Tobin NP, Harrell JC, Lövrot J, et al: Molecular subtype and tumor characteristics of breast cancer metastases as assessed by gene expression significantly influence patient post-relapse survival. Ann Oncol 26:81-88, 2015

80a. Giordano SH, Temin S, Kirshner JJ, et al: Systemic therapy for patients with advanced human epidermal growth factor receptor 2–positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 32:2078-2099, 2014

81. Prat A, Baselga J: The role of hormonal therapy in the management of hormonal-receptor-positive breast cancer with co-expression of HER2. Nat Clin Pract Oncol 5:531-542, 2008

82. Jeselsohn R, Buchwalter G, De Angelis C, et al: ESR1 mutations: A mechanism for acquired

endocrine resistance in breast cancer. Nat Rev Clin Oncol 12:573-583, 2015

83. André F, Cortés J: Rationale for targeting fibroblast growth factor receptor signaling in breast cancer. Breast Cancer Res Treat 150:1-8, 2015

84. Johnston SR: Enhancing endocrine therapy for hormone receptor-positive advanced breast cancer: Cotargeting signaling pathways. J Natl Cancer Inst 107:djv212, 2015

85. Azzoli CG, Baker S Jr, Temin S, et al: American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non–small-cell lung cancer. J Clin Oncol 27:6251-6266, 2009

86. Fagerlin A, Zikmund-Fisher BJ, Ubel PA: Helping patients decide: Ten steps to better risk communication. J Natl Cancer Inst 103:1436-1443, 2011

87. Butow PN, Dowsett S, Hagerty R, et al: Communicating prognosis to patients with metastatic disease: What do they really want to know? Support Care Cancer 10:161-168, 2002

88. Hagerty RG, Butow PN, Ellis PA, et al: Cancer patient preferences for communication of prognosis in the metastatic setting. J Clin Oncol 22:1721-1730, 2004

89. Lux MP, Bayer CM, Loehberg CR, et al: Shared decision-making in metastatic breast cancer: Discrepancy between the expected prolongation of life and treatment efficacy between patients and physicians, and influencing factors. Breast Cancer Res Treat 139:429-440, 2013

90. American Cancer Society: Cancer Facts & Figures for African Americans 2011-2012. www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-027765.pdf

91. American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity: Patient-centered care for older adults with multiple chronic conditions: A stepwise approach from the American Geriatrics Society—American Geriatrics Society Expert Panel on the care of older adults with multimorbidity. J Am Geriatr Soc 60:1957-1968, 2012

92. Howlader N, Krapcho M, Neyman N, et al (eds): SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). http://seer.cancer.gov/archive/csr/1975_2009_pops09/

93. US Cancer Statistics Working Group: United States Cancer Statistics: 1999–2008 Incidence and Mortality Web-Based Report. https://nccd.cdc.gov/uscs/

94. Mead H, Cartwright-Smith L, Jones K, et al: Racial and Ethnic Disparities in U.S. Health Care: A Chartbook. www.commonwealthfund.org/usr_doc/Mead_racialethnicdisparities_chartbook_1111.pdf

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Endocrine Therapy for Hormone Receptor–Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline

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