

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

Ann H. Partridge, R. Bryan Rumble, Lisa A. Carey, Steven E. Come, Nancy E. Davidson, Angelo Di Leo, Julie Gralow, Gabriel N. Hortobagyi, Beverly Moy, Douglas Yee, Shelley B. Brundage, Michael A. Danso, Maggie Wilcox, and Ian E. Smith

See accompanying editorial on page 3207 and article on page 3212

Author affiliations are found at the end of this article.

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Editor's note: This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, resources, and links to patient information at www.cancer.net, is available at http://www.asco.org/guidelines/ABC_HER2-negative_chemo.

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Corresponding author: American Society of Clinical Oncology, Address: 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

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A B S T R A C T

Purpose

To identify optimal chemo- and targeted therapy for women with human epidermal growth factor 2 (HER2)–negative (or unknown) advanced breast cancer.

Methods

A systematic review of randomized evidence (including systematic reviews and meta-analyses) from 1993 through to current was completed. Outcomes of interest included survival, progression-free survival, response, quality of life, and adverse effects. Guideline recommendations were evidence based and were agreed on by the Expert Panel via consensus.

Results

Seventy-nine studies met the inclusion criteria, comprising 20 systematic reviews and/or meta-analyses, 30 trials on first-line treatment, and 29 trials on second-line and subsequent treatment. These trials form the evidence base for the guideline recommendations.

Recommendations

Endocrine therapy is preferable to chemotherapy as first-line treatment for patients with estrogen receptor–positive metastatic breast cancer unless improvement is medically necessary (eg, immediately life-threatening disease). Single agent is preferable to combination chemotherapy, and longer planned duration improves outcome but must be balanced against toxicity. There is no single optimal first-line or subsequent line chemotherapy, and choice of treatment will be determined by multiple factors including prior therapy, toxicity, performance status, comorbid conditions, and patient preference. The role of bevacizumab remains controversial. Other targeted therapies have not so far been shown to enhance chemotherapy outcome in HER2–negative breast cancer.

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INTRODUCTION

The purpose of this Clinical Practice Guideline (CPG) is to provide treatment recommendations for women with locally advanced and/or metastatic (henceforth, “advanced”) breast cancer who are being considered for treatment with chemotherapy (CT) and/or targeted therapy. Breast cancer is the most prevalent cancer in women in the developed world, and it is the second most common cause of cancer-related death for women in the United States. It is estimated that in 2014 more than 232,000 women in the United States will be diagnosed with the disease, and 40,000 will die from it.¹ Long-term survival outcomes are related to disease stage at

presentation. Currently, the majority of patients presenting with localized disease will experience long-term disease-free survival, whereas those presenting with metastatic disease have a 5-year relative survival of only 24%² and almost none are cured.

The prognosis for patients with metastatic human epidermal growth factor receptor 2 (HER2)–positive breast cancer has improved significantly with the emergence of trastuzumab and other anti-HER2 agents (see companion American Society of Clinical Oncology [ASCO] guideline 1-07: Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer^{2a}), but the great majority of patients with advanced breast cancer have HER2–negative disease,

THE BOTTOM LINE

RECOMMENDATIONS FROM THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY FOR CHEMOTHERAPY AND TARGETED THERAPY FOR WOMEN WITH HER2-NEGATIVE (OR UNKNOWN) ADVANCED BREAST CANCER, BASED ON STANDARDIZED RATINGS OF CLINICAL BENEFITS, HARMS, EVIDENCE STRENGTH, AND RECOMMENDATION STRENGTH*

Guideline Questions

- This clinical practice guideline addresses the following four questions:
 1. What are the indications for chemotherapy versus endocrine therapy in ER-positive first relapse metastatic breast cancer?
 2. Is there an optimal first-line chemotherapy and/or targeted therapy regimen for patients with HER2-negative advanced breast cancer?
 - A. What is the optimal timing, dose, schedule, and duration?
 - B. Is there evidence to prefer single agent versus combination therapy?
 - C. Should first-line treatment vary by hormone receptor status, tumor subtypes (eg, luminal A v luminal B v triple negative) or clinical characteristics of the patient or tumor(s) (eg, site[s] or extent of metastasis, prior treatment, performance status and presence or absence of symptoms or immediately life-threatening disease)?
 3. Is there an optimal second- or greater-line chemotherapy and/or targeted therapy regimen?
 - A. What are the optimal timing, doses, schedules, and durations?
 - B. Is there evidence to prefer single agent versus combination therapy?
 - C. Should treatment regimen vary by tumor subtypes or clinical characteristics?
 4. At what point should anticancer therapy be discontinued?
 - A. Is there evidence to prefer maintenance versus interrupted therapy?

Target Population

- Women with advanced breast cancer (locally advanced/nonresectable or metastatic disease treated with noncurative intent). HER2-negative status is not an eligibility criterion for the systematic review, and for many patients in the trials reviewed, HER2 status was not given.

Target Audience

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

Methods

- An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

1. Endocrine therapy, rather than chemotherapy, should be offered as the standard first-line treatment for patients with hormone receptor–positive advanced/metastatic breast cancer, except for immediately life threatening disease or if there is concern regarding endocrine resistance.
 - A. The main benefit is less toxicity and better quality of life for the patient associated with endocrine therapy compared with chemotherapy (potential benefit: high). The harm is that metastatic disease could progress rapidly and prove fatal if there is no response, but the risk of this is low (potential harm: low).
 - B. The quality of the evidence is intermediate, and is based on the NCCC systematic review.
 - C. The strength of this recommendation is strong and is supported by the evidence and expert consensus.
- *Qualifying statement: It should be noted that the basis for this recommendation is the relative likelihood of response to chemotherapy versus endocrine therapy and not the rapidity of response, for which there are no good data*
2. Sequential single-agent chemotherapy rather than combination therapy should be offered, although combination regimens may be considered for immediately life-threatening disease for which time may allow only one potential chance for therapy.
 - A. The benefit is less toxicity and better quality of life (potential benefit: high). The potential harm is for rapidly progressing, life-threatening disease to escape control if response to a single agent isn't achieved (potential harm: high). The main benefit is there is less toxicity and better quality of life for the patient associated with sequential single agent chemotherapy compared with combination chemotherapy (potential benefit: high). The harm is that metastatic disease could progress rapidly if there is no response, but the risk of this is low (potential harm: low).
 - B. The evidence quality is high, and includes a large RCT.
 - C. The strength of this recommendation is strong.

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THE BOTTOM LINE (CONTINUED)

3. With regard to targeted agents, the role of bevacizumab is controversial, and this therapy should be considered (where available) with single-agent chemotherapy only when there is immediately life-threatening disease or severe symptoms, in view of improved response rates (similar to Recommendation 2 regarding the use of combination chemotherapy). It is recognized that there is not currently an approved indication for bevacizumab in the United States because the weight of evidence shows no significant survival benefit. Other targeted agents should not be used either in addition to, or as a replacement for, chemotherapy in this setting outside of a trial
 - A. The benefit is improved disease control (potential benefit: moderate). The potential harms are unique toxicity, increased costs, and barriers to access (potential harm: high)
 - B. The quality of the evidence is high and is supported by multiple trials.
 - C. The strength of the recommendation is moderate and is based on both evidence and expert consensus.
 - *Qualifying statement: Bevacizumab added to single-agent chemotherapy improves response and progression-free survival but not overall survival*
4. No single agent has demonstrated superiority in the treatment of patients with advanced breast cancer, and there are several active agents appropriate for first-line chemotherapy. The evidence for efficacy is strongest for taxanes and anthracyclines. Other options include capecitabine, gemcitabine, platinum-based compounds, vinorelbine, and ixabepilone. Treatment selection should be based on previous therapy, differential toxicity, comorbid conditions, and patient preferences. Specifically, drugs for which clinical resistance has already been shown should not be reused
 - A. The benefit is a patient-tailored approach with potential improvements in disease control and quality of life (potential benefit: high). The harm is the potential use of a less active agent (potential harm: low)
 - B. The evidence quality supporting the activity of a number of single agents is high, but there is insufficient evidence to support superiority of any single agent.
 - C. The strength of the recommendation is strong and is based on the available evidence and expert consensus
5. Chemotherapy should be continued until progression of disease as tolerated because it modestly improves overall survival and substantially improves progression-free survival, but this has to be balanced against toxicity and quality of life. Short breaks, flexibility in scheduling, or a switch to endocrine therapy (in patients with hormone receptor–positive disease) may be offered to selected patients.
 - A. The benefits are more time before disease-progression and modestly improved survival (potential benefit: high). The harm is more prolonged toxicity (potential harm: moderate).
 - B. The evidence quality is high, and is based on a systematic review with meta-analysis.
 - C. The strength of the recommendation is strong, and is supported by evidence and expert consensus.
 - *Qualifying statement: It is recognized that the balance between continuing treatment to maintain disease control and coping with progressive AEs and/or toxicity is a difficult one. It will be influenced by many factors, including drug used (eg, long-term use of capecitabine is relatively easy, whereas docetaxel is severely limited by cumulative toxicity) and requires a continuing dialogue between doctor and patient.*
6. Chemotherapy regimens should not be specifically tailored to different breast cancer subtypes (eg, triple negative, lobular) at the present time due to the absence of evidence proving differential efficacies. In addition, in vitro chemoresistance assays should not be used to select treatment
 - A. The benefits are not omitting potentially efficacious treatment and cost-saving on in vitro assays (potential benefit: high)
 - B. Current evidence shows no convincing basis for either of these approaches
 - C. The strength of this recommendation is moderate, and is supported by expert consensus
 - *Qualifying statement: This recommendation will need to be modified if ongoing or future research addressing this important issue suggests benefits of tailoring*
7. Second- and later-line therapy may be of clinical benefit and should be offered as determined by previous treatments, toxicity, coexisting medical conditions, and patient choice. As with first-line treatment, no clear evidence exists for the superiority of one specific drug or regimen. Active agents include those active in first-line treatment.
 - A. The benefit is further chance of disease control and symptomatic improvement (potential benefit: high). The harm is toxicity (potential harm: high).
 - B. The quality of the evidence ranges from high to low as reported in multiple randomized trials.
 - C. The strength of the recommendation is strong and is based on expert consensus

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THE BOTTOM LINE (CONTINUED)

- *Qualifying statement: The most convincing data are for eribulin based on survival superiority against best standard treatment in a recent large RCT, but there is a lack of good comparative data between these various agents.*
8. Palliative care should be offered throughout the continuum of care. As there are diminishing returns with later lines of chemotherapy, clinicians should also offer best supportive care without further chemotherapy as an option.
 - A. The benefits include a patient-centered approach emphasizing quality of life (potential benefit: high). The main harm is fear of abandonment and giving up hope, which can be addressed by effective communication and appropriate end-of-life planning (potential harm: moderate).
 - B. The quality of the evidence is intermediate and is supported by several RCTs in patients with advanced cancer.
 - C. The strength of the recommendation is strong and is supported by evidence, expert consensus, and another independent expert consensus.⁹
 - *Qualifying statement: Evidence suggests that response to second and subsequent lines of chemotherapy is strongly influenced by response to earlier treatment; patients whose disease has failed to respond to up to two initial lines of treatment are less likely to respond to a third or subsequent line.¹⁰*
 9. As there is no cure yet for patients with advanced breast cancer, clinicians should encourage all eligible patients to enroll onto clinical trials. This should include the option of phase II and even targeted phase I trials before all standard lines of therapy have been used, in the absence of immediately life-threatening disease.
 - A. The benefits are more patients will be directed to clinical studies providing treatment benefits to them, and the medical community will benefit from more research to improve treatments available and on which to base treatment decisions. The potential harm is patients will receive inferior treatment.
 - B. There is no strong evidence to suggest this approach might impair outcome.
 - C. The strength of this recommendation is strong and based on expert consensus.

Additional Resources

- More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and resources, is available at www.asco.org/guidelines/ABC_HER2-negative_chemo. Patient information is available at www.cancer.net.
- * Criteria for ratings of clinical benefits, harms, strength of evidence, and strength of recommendations are shown in the Methodology Supplement.

for which emergence of effective new targeted therapies is beginning (eg, everolimus) but has lagged. A significant minority of these patients have tumors that are negative for all three prognostic/predictive biomarkers—HER2, estrogen receptor (ER), and progesterone receptor (PR), referred to as “triple negative”—comprising a patient group with a relatively poor prognosis. However, the majority of patients with advanced breast cancer will have ER-positive, HER2-negative disease, often with a relatively indolent course. So, the absolute number of patients involved and the relatively slow natural history mean that HER2-negative advanced breast cancer represents one of the most prevalent cancer problems currently facing the developed world. This guideline presents evidence and best-practice recommendations for women with HER2-negative advanced breast cancer who may benefit from CT. It should be noted that although we have had to include a HER2-unknown group for earlier trials for which HER2 data were unavailable, we nevertheless consider it mandatory now for all patients to have HER2 (and of course ER) status determined in their cancers. If this is not available from the primary cancer, and to confirm that a lesion is indeed advanced breast cancer, then a biopsy of a metastatic site must be done. Indeed, we consider it increasingly desirable for a metastatic biopsy to be done anyway because ER and/or HER2 status may change. However, at present,

there is a lack of clear evidence that the expression of biomarkers of metastatic lesion is predictive of response to therapy in this setting.

At present, advanced breast cancer remains an incurable disease, and the general goals of therapy are to prolong survival, palliate symptoms, and optimize quality of life (QoL). There are many agents available for the systemic treatment of breast cancer that may result in tumor response or stability; however, most antineoplastic agents are also associated with adverse events (AEs) that may impair QoL and even cause life-threatening toxicity. Despite the development of many new agents, it has often been difficult to demonstrate an overall survival (OS) advantage from any given regimen in this setting, partly because of the opportunity for women to cross over to other treatments after a study, and partly because of the heterogeneity of prior treatment and of the disease itself. Further, only recently have investigators begun to take tumor subtype into account when designing and conducting clinical trials in this setting.

Accordingly, when selecting treatment for a given individual with metastatic breast cancer, one must consider not only data on efficacy, but also the toxicity profile; the patient's performance status and comorbid conditions; prior therapy received; the pace of the patient's disease (eg, indolent disease *v* immediately life-threatening disease); and the patient's preferences regarding additional therapy, anticipated

AEs, as well as schedule and dosing mode. The optimal first-line or later-line CT choice may therefore vary considerably between individual patients.

This CPG is intended to provide clinical recommendations based on both on a systematic review of the most recent evidence and on the incorporation of older data and reviews. Given the longstanding history of studies performed in this population, we used a previously published rigorous systematic review conducted in 2009 by the National Collaborating Centre for Cancer³ (NCCC, United Kingdom) as a starting point for updating the literature search, particularly with regard to the role of CT versus endocrine therapy as first-line therapy for hormone receptor–positive disease, and consideration of first-line CT. From this starting point, we have added additional evidence published since 2008 for first-line studies, and evidence from 1993 onward for second- and subsequent-line studies for this CPG. We have also included evidence on QoL outcomes and AEs.

Prior Data

Chemotherapy versus endocrine therapy. The prior systematic review³ addressed the role of endocrine therapy compared with CT as first-line treatment for advanced hormone receptor–positive breast cancer. One high-quality systematic review⁴ was used to form recommendations, which entailed an analysis of 10 randomized controlled trials (RCTs) comparing CT with endocrine treatments. In that review, no difference was found in OS, and no data were available on QoL or AEs, but the authors report that CT was associated with higher levels of toxicity, especially nausea, vomiting, and alopecia. They recommended endocrine therapy first unless disease was rapidly progressing, in which case CT was appropriate, as a fast response was medically necessary.

Single-agent versus combination CT. The prior NCCC review also presented data regarding single-agent versus combination CT studies, single-agent sequences versus combination studies, as well as data from trials of the use of specific agents used alone or in combination in later lines of therapy. Some of the key findings from that review are described here.

An RCT comparing first-line sequential single-agent versus combination treatment reported by Sledge et al,⁵ included a total of 731 patients randomly assigned to one of three arms: doxorubicin and paclitaxel together, doxorubicin until progression then paclitaxel, or paclitaxel until disease progression then doxorubicin. Tumor response rate and time to treatment failure (TTF) were significantly lower in either of the two sequential arms when compared with the combined therapy, but they did not differ from each other. There were, however, no significant differences between the duration of OS between arms, and the combination arm was associated with more severe adverse effects.

The NCCC review also reported that combination regimens were associated with a survival benefit compared with single-agent regimens in the first-line setting, but noted that these conclusions were limited by lack of control for subsequent treatments and lack of QoL data. There is evidence from a pivotal trial reported by O'Shaughnessy et al,⁶ as well as the two follow-up articles reported by Leonard et al⁷ and Miles et al⁸ that single-agent sequential therapy is likely no different from combination regimens, although combination regimens are associated with greater, and more severe, AEs.

For second-line treatment options, the evidence included in the NCCC review was generally weaker, comprising smaller trials with fewer patients. For second-line or greater treatment options including vinorelbine, reported response rates ranged from 50% to 90% when given alone or in combination with trastuzumab, docetaxel, or capecitabine. For capecitabine, several trials were obtained describing its use in the second-line or greater setting, and this body of evidence was considered low quality, comprising noncomparative studies with few patients. In these studies, reported response rates ranged from 10% to 42%, median OS ranged from 9.4 to 18.1 months, median response duration from 3.8 to 15.4 months, and median TTP from 3.5 to 6.6 months. However, 21% of all patients experienced grade 3 or 4 hand-foot syndrome. For taxane-containing treatment in the second line or greater, given either alone or in combination, no benefit was reported for women who entered the trials anthracycline naive. Meta-analysis detected significant improvements in OS, TTP, tumor response, and TTF favoring taxane-containing regimens compared with nontaxane regimens. However, the benefits detected for OS and TTP were lost when only first-line therapy with taxanes was considered. Taxanes and taxane-containing regimens are associated with higher incidences of neurotoxicity and leukopenia but fewer cases of nausea and vomiting than controls.

Findings from the prior NCCC systematic review detailed above combined with results from this updated review, as well as consensus of the Expert Panel, inform the recommendations of this CPG focused on optimal therapy for women with advanced HER2-negative breast cancer.

GUIDELINE QUESTIONS

1. What are the indications for CT versus endocrine therapy in ER-positive first-relapse metastatic breast cancer?
2. Is there an optimal first-line CT and/or targeted therapy regimen for patients with HER2-negative advanced breast cancer?
 - A. What is the optimal timing, dose, schedule, and duration?
 - B. Is there evidence to prefer single-agent versus combination therapy?
 - C. Should first-line treatment vary by hormone receptor status, tumor subtypes (eg, luminal A v luminal B v triple negative), or clinical characteristics of the patient or tumor (eg, site[s] or extent of metastasis, prior treatment, performance status, and presence or absence of symptoms or immediately life-threatening disease)?
3. Is there an optimal second- or greater-line CT and/or targeted therapy regimen?
 - A. What are the optimal timing, doses, schedules, and durations?
 - B. Is there evidence to prefer single-agent versus combination therapy?
 - C. Should treatment regimen vary by tumor subtypes or clinical characteristics?
4. At what point should anticancer therapy be discontinued?
 - A. Is there evidence to prefer maintenance versus interrupted therapy?

METHODS

Panel Composition

The ASCO Clinical Practice Guidelines Committee convened an Expert Panel with multidisciplinary representation in medical oncology, community oncology, patient representation, and guideline methodology. The Expert Panel members are listed in Appendix 1 (online only).

Guideline Development Process

The Expert Panel, who met 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 in consideration of the evidence. Members of the Expert Panel are responsible for drafting the penultimate version of the guideline, which is then circulated for external review and submitted to *Journal of Clinical Oncology (JCO)* 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 Conflict of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines (“Procedures,” summarized at <http://www.asco.org/rwc>). Members of the Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, 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 relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Panel did not disclose any such relationships.

Literature Review

ASCO guidelines are based on systematic reviews of the literature. A protocol for each systematic review defines parameters for a targeted literature

search. Additional parameters include relevant study designs, literature sources, types of reports, and prespecified inclusion and exclusion criteria for identified literature. This guideline protocol was reviewed and approved by the ASCO Clinical Practice Guidelines Committee's Methodology Subcommittee

Literature Search Strategy

For this CPG, the recommendations were developed by an Expert Panel with multidisciplinary representation using a systematic review (January 2009 through to May 2013 for first-line trials; January 1993 through to May 2013 for second-line trials) of systematic reviews with or without meta-analysis, meta-analyses, RCTs, and clinical experience.

Study Selection Criteria

Articles were selected for inclusion in the systematic review of the evidence on the basis of the following criteria:

- Included women 18 years of age and older with HER2-negative (or unknown) advanced breast cancer.
- Were fully published reports identified using the MEDLINE (OVID) database or abstracts from specific conference proceedings (San Antonio Breast Cancer Symposium; 2011, 2012) and ASCO abstracts (2012, 2013).
- Included a minimum of 25 patients per study arm.
- Were published in English.

RESULTS

A total of 78 studies met the eligibility criteria and form the evidentiary basis for the guideline recommendations, comprising 20 systematic reviews and/or meta-analyses¹¹⁻³⁰ (Table 1), 30 studies reporting on first-line treatment options,³¹⁻⁶⁰ and 28^{6,31,39,61-85} reporting on second-line or greater treatment options (Table 2). Two^{31,39} of the included studies reported on both first- and second-line treatment and are included in both sections.

Systematic Reviews and/or Meta-Analyses

Twenty¹¹⁻³⁰ systematic reviews (with or without meta-analysis) and/or meta-analyses of various rigor and quality were obtained. As none were deemed suitable as the basis for recommendations, a formal assessment of quality was not performed. Table 1 provides a summary of main findings. The key points relating to this CPG are as follows:

- Over the past 30 years, OS has improved with the addition of new drugs,^{22,23} although progression-free survival (PFS) and TTP remain virtually unchanged.²³
- Longer planned treatment durations have been associated with significant increases in OS and PFS.¹⁸
- Combination therapy has demonstrated increases in treatment response rates,^{15,16} but not in OS, compared with single-agent regimens.
- High-dose CT regimens have demonstrated improvements in event-free survival but no clear improvement in OS.²⁴
- The addition of bevacizumab to CT has demonstrated improvements in objective response rate (ORR) and PFS^{17,26,28} but not in duration of response^{17,26,28} or OS. One study reported no differences in AEs associated with the addition of bevacizumab,²⁶ whereas another reported increased rates of hypertension.¹⁷
- Anthracyclines plus taxanes are no more effective than anthracyclines plus cyclophosphamides for any outcomes.²⁹
- Capecitabine has demonstrated superior median survival compared

CT and Targeted Therapy for HER2-Negative (or unknown) ABC

Table 1. Main Findings From Systematic Reviews and/or Meta-Analyses

Study	Publication Type	Evidence Base	Main Findings
Petrelli et al, 2012 ²⁶	Meta-analysis	Two studies including 1,003 patients,	<ul style="list-style-type: none"> ● Addition of bevacizumab to CT regimens resulted in significant increases in ORR and PFS. ● No differences detected in duration of responses. ● Addition of bevacizumab did not increase adverse events (in particular febrile neutropenia). ● Bevacizumab should be investigated further in the second-line setting.
O'Shaughnessy et al, 2012 ²⁵	Systematic review	Seven prospective studies including 1,813 patients and four retrospective studies including 1,087 patients	<ul style="list-style-type: none"> ● First-line capecitabine monotherapy demonstrated superior median survival compared with CMF combination therapy; all other comparisons for efficacy were nonsignificant. ● Capecitabine monotherapy (1,000 mg/m² twice daily, for 14 d of a 21-d cycle) has proven efficacy in the first-line setting with acceptable adverse effects (lower myelosuppression), allowing for further cycles.
Mukonje et al, 2012 (ASCO abstract) ²³	Systematic review	134 RCTs including 38,090 patients	<ul style="list-style-type: none"> ● OS in patients with advanced breast cancer continues to improve, and the authors speculate this has to do with more tolerable combination regimens and an increase in the number of cycles patients are offered. ● PFS and TTP have remained unchanged over the last 30 yr.
Blum et al, 2011 (SABC abstract) ¹⁴	Meta-analysis	Two RCTs including 268 patients (first line), and five RCTs including 537 patients (second line)	<ul style="list-style-type: none"> ● Patients receiving capecitabine monotherapy for anthracycline plus taxane pretreated advanced breast cancer demonstrated superior ORR and OS in first-line compared with second-line treatment.
Belfiglio et al, 2012 ¹³	Meta-analysis	Three RCTs including 1,313 patients	<ul style="list-style-type: none"> ● Comparisons made between docetaxel monotherapy and combinations including docetaxel detected superior TTP with the combination arms, but no differences in ORR or OS. ● Combination docetaxel treatment was associated with higher incidences of grade 3 diarrhea and stomatitis.
Xu et al, 2011 ³⁰	Meta-analysis	Four RCTs including 2,343 patients	<ul style="list-style-type: none"> ● Comparisons made between taxane monotherapy and combinations including taxanes detected superior PFS and PR with the combination arms, but no differences were detected in 1-yr survival, clinical benefit rate, or CR. ● Monotherapy was associated with significantly lower stomatitis and diarrhea.
Vriens et al, 2011 (SABCS abstract) ²⁹	Meta-analysis	Five RCTs in the metastatic setting (of 10 RCTs total), No. of patients NR.	<ul style="list-style-type: none"> ● Pooling five RCTs that compared an anthracycline plus a taxane with an anthracycline plus a cyclophosphamide detected no difference in OS. ● No difference in efficacy was detected between taxanes and cyclophosphamide.
Gennari et al, 2011 ¹⁸	Systematic review with meta-analysis	11 RCTs including 2,269 patients	<ul style="list-style-type: none"> ● Longer treatment durations were associated with significant improvements in OS and PFS.
Cuppone et al, 2011 ¹⁷	Meta-analysis	Five RCTs including 3,841 patients	<ul style="list-style-type: none"> ● Adding bevacizumab to first-line combination regimens significantly improved PFS but at a cost of significantly higher incidences of hypertension.
Aapro et al, 2011 ¹¹	Meta-analysis	Two studies including 114 patients	<ul style="list-style-type: none"> ● Weekly NAB-paclitaxel is superior to an every 3 weeks schedule for ORR and PFS.
Valachis et al, 2010 ²⁸	Meta-analysis	Five RCTs including 3,163 patients	<ul style="list-style-type: none"> ● Adding bevacizumab to first-line combination regimens significantly improved PFS and ORR
Mauri et al, 2010 ²¹	Systematic review with meta-analysis	11 trials including 2,540 patients	<ul style="list-style-type: none"> ● When comparing weekly paclitaxel with paclitaxel every 3 weeks, the following significant differences were detected: <ul style="list-style-type: none"> ● Weekly paclitaxel demonstrated superior OS ● Paclitaxel every 3 weeks demonstrated superior ORR ● No differences in PFS were detected ● When comparing weekly docetaxel with docetaxel every 3 weeks, no significant differences were detected between ORR, PFS, or OS. ● Serious adverse events, neutropenia, neutropenic fever, and peripheral neuropathy were significantly lower in weekly taxanes schedules. ● The incidence of nail changes and epiphora were significantly lower in the every 3 weeks docetaxel regimens.
Li et al, 2010 ²⁰	Systematic review	Two RCTs including 1,953 patients	<ul style="list-style-type: none"> ● For patients with metastatic or locally advanced breast cancer who experienced disease progression while on or following an anthracycline with a taxane treatment, ixabepilone plus capecitabine demonstrated improvements in OS, TTP, and ORR compared with capecitabine alone. ● Peripheral neuropathy, myalgia, and neutropenia were more common with ixabepilone combination therapy.

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Table 1. Main Findings From Systematic Reviews and/or Meta-Analyses (continued)

Study	Publication Type	Evidence Base	Main Findings
Butters et al, 2010 ¹⁵	Systematic review	17 trials including 2,674 patients	<ul style="list-style-type: none"> • In comparisons between two-drug combinations and three or more drug combinations, no differences were detected for OS or TTP, although differences were detected in ORR. • An increase in the number of drugs was associated with an increase in the incidence of adverse effects.
Al-Batran et al, 2010 ¹²	Systematic review with meta-analysis	Four RCTs including 274 patients	<ul style="list-style-type: none"> • Anthracycline rechallenge with pegylated liposomal doxorubicin is effective in patients with metastatic breast cancer who have a favorable performance status, regardless of setting, resistance, cumulative dose, or time since prior conventional anthracycline therapy as determined by assessing CBR.
Nieto et al, 2009 ²⁴	Meta-analysis	15 RCTs including 6,102 patients	<ul style="list-style-type: none"> • Pooling detected an absolute 13% event-free survival benefit in favor of high-dose CT at a median 6-yr follow-up. • Pooling breast cancer-specific survival and OS did not detect significant differences.
Jassem et al, 2009 ¹⁹	Systematic review	Five RCTs including 1,178 patients	<ul style="list-style-type: none"> • No RCT reported an OS difference between arms. • Gemcitabine plus vinorelbine demonstrated superior PFS compared with vinorelbine alone. • Capecitabine plus bevacizumab demonstrated superior ORR compared with capecitabine alone. • Median OS for these patients typically remained < 16 mo.
Carrick et al, 2009 ¹⁶	Systematic review	43 trial including 9,742 patients	<ul style="list-style-type: none"> • When comparing single-agent regimens with combination regimens, significant differences were detected in favor of combination regimens for OS, TTP, and ORR. • Combination regimens were associated with increases in adverse effects in white cell count, alopecia, nausea, and vomiting.
Piccart-Gebhart et al, 2008 ²⁷	Systematic review with meta-analysis	11 RCTs including 3,953 patients	<p>Pooling trials comparing taxanes against combinations of taxanes plus anthracyclines found:</p> <ul style="list-style-type: none"> • Single-agent taxane regimens were superior to single-agent anthracycline regimens for OS and ORR, but demonstrated inferior PFS. • Combination regimens with taxanes demonstrated superior ORR and PFS, but inferior OS.
Mauri et al, 2008 ²²	Systematic review with meta-analysis	370 trial including 54,189 patients	<ul style="list-style-type: none"> • Compared against older non-anthracycline regimens, newer anthracycline regimens demonstrate 22%-33% improvements in RRR. • Other newer regimens (single-agent taxane, combinations of anthracyclines with taxanes, taxanes with capecitabine or gemcitabine, and molecular targeted agents) demonstrated further benefits in RRR. • The regimens had similar efficacy profiles (< 5% difference in HR for RRR) as first- and subsequent-line therapies.

Abbreviations: CBR, clinical benefit rate; CMF, cyclophosphamide, methotrexate, fluorouracil; CR, complete response; CT, chemotherapy; HR, hazard ratio; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RCT, randomized clinical trial; RRR, relative risk reduction; SABCS, San Antonio Breast Cancer Symposium; TTP, time to progression.

with cyclophosphamide-methotrexate-fluorouracil (CMF), with an acceptable toxicity profile,²⁵ and further benefits have been found when combining capecitabine with bevacizumab.¹⁹

- Taxane combination regimens were superior to taxane monotherapy for TTP,¹³ PFS,³⁰ and partial response³⁰ rates but not for OS. Furthermore, taxane monotherapy was associated with significantly fewer AEs, especially grade 3 and higher stomatitis and diarrhea.^{13,27,30}

Overview

Thirty³¹⁻⁶⁰ RCTs (both phase III and randomized phase II) reporting on first-line treatment (covering the years 2009 through 2013) along with 28^{6,31,39,61-85} RCTs (both phase III and randomized phase II) reporting on second-line treatment (covering the years 1993 through 2013) were identified in the literature search. As a result of the lack of a standard first-line treatment for patients with advanced breast cancer, the trials compared various regimens and reported on various primary outcomes related to efficacy, quality

of life, and AEs. Table 2 reports the efficacy outcomes, Table 3 reports Quality of Life outcomes, Table 4 reports on acute and chronic adverse effects.

Study Characteristics

Details on the study characteristics of all 30 of the included first-line trials,³¹⁻⁶⁰ involving a total of 10,675 patients (minimum 78⁵⁵; maximum: 1,237⁵⁰) can be found in the Data Supplement. The majority of the trials included patients with Eastern Cooperative Oncology Group performance status (PS) 0 to 2 (or equivalent), although 11 trials^{31,32,34,40,45,48-51,54,55} only included patients with PS 0 to 1 (representing a healthier population), and two trials^{39,57} included patients with PS 0 to 3 (representing a more at-risk population). Median ages included in the trials ranged from a low of 51 years⁴⁷ to a high of 74 years.⁵⁵ While most of the trials that reported on menopausal status reported proportions of premenopausal patients of approximately 20%, this ranged from a low of 11.8%⁴⁴ to a high of 54.3%.³⁵ Patients reported as being either ER positive or PR positive ranged from a low

Table 2. Efficacy Outcomes

Source	Intervention/Comparisons	End Points	No. of Patients Evaluated	Survival			Overall Response	CBR ^a
				OS	PFS			
First-Line Treatment: Single-Agent v Single-Agent Regimens								
Gradishar et al, 2012 ³⁷	NAB-paclitaxel 300 v	Primary: ORR; secondary: DCR, PFS, duration of response, OS	76	Median: 27.7 months	NR	NR	NR	NR
	NAB-paclitaxel 100 v		76	22.2 months				
	NAB-paclitaxel 150 v		74	33.8 months				
	Docetaxel 100 every 3 weeks		74	26.6 months; <i>P</i> < .05 in favor of 150 compared with all others				
First-Line Treatment: Single-Agent v Combination Regimens								
Bergh et al, 2012 ³²	Docetaxel + sunitinib (SD) v Docetaxel (D)	Primary: PFS; secondary: ORR, duration of response, OS, safety	296	1-yr: 81% 84%; <i>P</i> = ns	Median: 8.6 months 8.3 mo; <i>P</i> = ns	S + D, 55% v D, 42%; <i>P</i> < .05	NR	NR
	Intermittent capecitabine v Continuous capecitabine vs CMF	PFS (median)	107 107 109 (323)	Median: 22 months 18 months; <i>P</i> < .05 in favor of capecitabine	Median: 6 months 6 months; <i>P</i> = ns	22% 20% 18%; <i>P</i> = ns	NR	NR
Katsumata et al, 2009 ³⁸	Doxorubicin + cyclophosphamide (AC) v Docetaxel (D) v Alternating treatment with AC-D	Primary: TTF; secondary: OS, PFS, ORR, AEs	146 147 148	Median: 22.4 months 25.7 months 25.0 months <i>P</i> = ns	Median: 6.6 months 7.0 months 7.1 months; <i>P</i> = ns	29% 40% 35%; <i>P</i> < .05, D > AC	NR	NR
	First-Line Treatment: Combination v Combination Regimens							
Lam et al, 2013 (ASCO abstract) ⁴¹	Paclitaxel + bevacizumab → capecitabine v Paclitaxel + bevacizumab + capecitabine → bevacizumab + capecitabine	PFS	NR	Median: 23.1 months 24.1 months; <i>P</i> = ns	8.4 months 11 months; <i>P</i> < .001 ATX > AT	50% 67%, <i>P</i> = N;R	NR	NR
	Capecitabine + sorafenib v Capecitabine + PL	Primary: PFS secondary: OS, TTP, ORR, duration of response, safety	100 99	Median: 22.8 months 18.3 months; <i>P</i> = ns	Median: 7.6 months 4.1 months; <i>P</i> < .05	NR	NR	NR
Rugo et al, 2012 (ASCO 2012) ⁵²	Paclitaxel ± bevacizumab v Albumin-bound paclitaxel ± bevacizumab v Ixabepilone ± bevacizumab	PFS	283 271 245	NR Median: 10.4 months 9.6 months 7.6 months <i>P</i> v NP; <i>P</i> = ns; <i>P</i> v IX, <i>P</i> < .05 in favor of P	NR months months	NR	NR	NR
Robert et al, 2011 (RIBBON-1 trial) ⁵⁰	Capecitabine + PL or Capecitabine + bevacizumab or Taxane/anthracycline + PL or Taxane/anthracycline + bevacizumab	Primary: PFS; secondary: ORR, OS, 1-yr survival, duration of response, safety	206 409 207 415	1-yr: 74.4% 81.0% 83.2% 80.7%; <i>P</i> = ns for all four groups	6.2 months 9.8 months; <i>P</i> < .05, BV > PL 8.3 months 10.7 months; <i>P</i> < .05, BV > PL	23.6% 35.4% 37.9% 51.3%	NR	NR

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Table 2. Efficacy Outcomes (continued)

Source	Intervention/Comparisons	End Points	No. of Patients Evaluated	Survival			Overall Response	CBR ^a
				OS	PFS			
Robert et al, 2011 ⁵¹	Paclitaxel + sunitinib v Paclitaxel + bevacizumab	Primary: PFS; secondary: ORR, duration of response, OS, 1- and 3-yr survival, safety.	242 243 (485)	At 8.1 mo (cut-off): 79% 87%; <i>P</i> < .05 in favor of <i>P</i> + B	Median: 7.4 months 9.2 months; <i>P</i> < .5 in favor of <i>P</i> + B	32.2% 32.1%; <i>P</i> = ns	NR	
O'Shaughnessy et al, 2011 ⁴⁸	Gemcitabine + carboplatin + iniparib v Gemcitabine + carboplatin	Primary: CBR; secondary: ORR, PFS	57 59	Median: 12.3 months 7.7 months; <i>P</i> < .05	Median: 5.9 months 3.6 months <i>P</i> < .05	52% 32%; <i>P</i> < .05	56% 34%; <i>P</i> < .05	
Miles et al, 2010 (AVADO trial) ⁴⁵	Docetaxel + bevacizumab 7.5 v Docetaxel + bevacizumab 15 v Docetaxel with PL	Primary: PFS; secondary: ORR, duration of response, TTF, OS, safety, QoL	248 247 241	1 yr: 81% 84% 76%; <i>P</i> < .05, DB15 > D	Median: 9 months 10.1 months 8.2 months; <i>P</i> < .05, DB15 > D	55.2% 64.1% 46.4%; <i>P</i> < .05, DB15 > D	NR	
Second-Line Treatment: Single-Agent v Single-Agent Regimens								
Barrios et al, 2010 ⁶³	Sunitinib v Capecitabine	Primary: PFS; secondary: TTP, ORR, duration of response, OS, safety	238 244	Median: 15.3 months 24.6 months; <i>P</i> = ns	Median: 2.8 months 4.2 months; <i>P</i> < .05	11% 16%; <i>P</i> = ns	19% 27%; <i>P</i> < .05	
Jones et al, 1995 ⁷¹	Vinorelbine Melphalan	Primary: TTP, QoL; secondary: TTF, ORR	115 64	Median: 35 weeks 1-yr: 35.7% 31 weeks <i>P</i> < .05 21.7% <i>P</i> < .05	NR	16% 9%; <i>P</i> = ns	NR	
Second-Line Treatment: Single-Agent v Combination Regimens								
Sparano et al, 2010 ⁶³	Ixabepilone + capecitabine v Capecitabine alone	Primary: OS; secondary: PFS, ORR, TTF, safety	609 612	Median: 16.4 months 15.6 months <i>P</i> < .05	Median: 6.2 months 4.4 months; <i>P</i> < .05	43.3% 28.8%; <i>P</i> < .05	NR	
Albain et al, 2008 ⁶²	Gemcitabine + paclitaxel v Paclitaxel monotherapy	Primary: OS	266 263	Median: 18.6 months 15.8 months; <i>P</i> < .05	NR	41.4% 26.2%; <i>P</i> < .05	NR	
Miller et al, 2005 ⁷⁵	Capecitabine v Capecitabine + bevacizumab	Primary: PFS; secondary: ORR, CoL, survival	230 232	Median: 14.5 months 15.1 months; <i>P</i> = ns	HR = 0.98; <i>P</i> = ns	9.1% 19.8%; <i>P</i> < .05	NR	
Reyno et al, 2004 ⁷⁹	BMS-217380-01 + doxorubicin v Doxorubicin alone	NR	153 152	Median: 23.6 months 15.6 months; <i>P</i> < .05	Median: 5.9 months 6.0 months; <i>P</i> = ns	35.5% 36.5%; <i>P</i> = ns	NR	
O'Shaughnessy et al, 2002 ⁶	Capecitabine + docetaxel v Docetaxel alone	Primary: TTP; secondary: ORR, OS	255 256	1-yr: 57% 47%; <i>P</i> < .05	Median: 6.1 months 4.2 months; <i>P</i> < .05	42% 30%; <i>P</i> < .05	NR	
Nabholtz et al, 1999 ⁷⁷	Docetaxel v Mitomycin + vinblastine	Primary: ORR, TTP	203 189	Median: 11.4 months 8.7 months <i>P</i> < .05	NR	30% 11.6%; <i>P</i> < .05	NR	

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Table 2. Efficacy Outcomes (continued)

Source	Intervention/Comparisons	End Points	No. of Patients Evaluated	Survival		
				OS	PFS	Overall Response
Baselga et al, 2012 ³¹	Capecitabine + sorafenib v Capecitabine + placebo	Primary: PFS; secondary: OS, TTP, ORR, duration of response, safety	100	Second-Line Treatment: Combination v Combination Regimens		
				Median: 19.0 months 23.4 months; <i>P</i> < .05	Median: 5.7 months 4.1 months; <i>P</i> < .05	NR
Cortes et al, 2011 (EMBRACE) ⁶⁷	Eribulin monotherapy Treatment of physician's choice	NR	459	Second-Line Treatment: Single-Agent or Combination Regimen v Control, BSC, or Observation		
				Median: overall: 13.1 months 46%	Median: 3.7 months	12%
Alba et al, 2010 ⁶¹	Pegylated liposomal doxorubicin v Observation	Primary: TTP	216	Second-Line Treatment: Single-Agent or Combination Regimen v Control, BSC, or Observation		
				10.6 months; <i>P</i> < .05; 42%; <i>P</i> < .05	2.2 months; <i>P</i> = ns	5%; <i>P</i> < .05
			78	Median: 24.8 months	Median TTP: 8.4 months	NR
			77	22.0 months <i>P</i> = ns	5.1 months; <i>P</i> < .05	NR

Abbreviations: AE, adverse event; ANZBCTG, Australia & New Zealand Breast Cancer Trials Group; BSC, best supportive care; CMF, cyclophosphamide, methotrexate, fluorouracil; DCR, XXXX; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PL, placebo; QoL, quality of life; TTF, time to treatment failure; TTP, time to progression.

Table 3. Quality of Life

Source	Intervention/Comparisons	No. of Patients Evaluated	QoL Instrument	Summary Score	Subscale Summary Score	Subscale Summary Score
Cella et al, (2011 E2100 trial) ³⁶	Paclitaxel 90 v	315	FACT-B (FACT-G and BCS)	NR	FACT-BCS Baseline: 23.5, at 17 weeks: 22.66, at 33 weeks: 22.41	All FACT-G comparisons were $P = ns$
	Paclitaxel 90 + bevacizumab	341			Baseline: 23.99, $P = ns$; at 17 weeks: 23.75 $P < .05$; $P + B > P$ at 33 weeks: 24.08, $P < .05$, $P + B > P$	
Svensson et al, (2012 TEX trial) ⁵⁹	Epirubicin + paclitaxel (ET) v epirubicin + paclitaxel + capecitabine (TEX)	252	EORTC QLO-C30	Global health: HR: 0.92 (95% CI, 0.85 to 0.99); $P < .05$, response	Physical functioning: HR: 0.92 (95% CI, 0.86 to 0.99); Role functioning HR: 0.94 (95% CI, 0.89 to 0.99); Fatigue: HR: 1.12 (95% CI, 1.04 to 1.20); Pain: HR: 1.08 (95% CI, 1.02 to 1.15); Dyspnea: HR: 1.05 (95% CI, 1.00 to 1.12); Appetite loss: HR: 1.05 (95% CI, 0.99 to 1.11), bold indicates $P < .05$ for response	NR
Nuzzo et al, 2011 ⁴⁷	Docetaxel + epirubicin if previously treated with adjuvant anthracyclines or docetaxel + capecitabine if previously treated with adjuvant anthracyclines (every 3 weeks) v Docetaxel + epirubicin if previously treated with adjuvant anthracyclines or docetaxel + capecitabine if previously treated with adjuvant anthracyclines (weekly)	69	EORTC QLO-C30	67.9	Physical functioning, emotional functioning, cognitive functioning, social functioning, all $P_s = ns$	Role functioning: 84.0
		66		60.0; $P < .05$		72.0; $P < .05$
Brufsky et al, 2011 ⁸⁴	Paclitaxel + bevacizumab v Paclitaxel + bevacizumab + gemcitabine	94	FACT-B	PB superior to PB + G, $P < .05$	Social/family well-being, breast cancer additional concerns, both $P_s < .05$, PB > PB + G	NR
		93				
Svensson et al, 2010 ⁵⁸	Epirubicin + paclitaxel (ET) v Epirubicin + paclitaxel + capecitabine (TEX)	143	EORTC QLO-C30 and QLO-BR23	Global health (QL2): at baseline, $P < .05$; at 2 months, $P = ns$; at 9 months, $P < .05$, TEX > ET (60.2 v 50.0)	Physical functioning: at baseline, $P < .05$; at 2 months, $P = ns$; at 9 months, $P < .05$, TEX > ET (77.8 v 68.9)	Role functioning: at 2 months, $P < .05$, ET > TEX (45.1 v 38.9); at 9 months, $P = ns$
		144				

Abbreviations: EORTC-QLO-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-B, Functional Assessment of Cancer Therapy-Breast; FACT-BCS, FACT Breast Cancer Subscale; FACT-G, FACT General; HR, hazard ratio; NR, not reported; QoL, quality of life; QLO-BR23, EORTC Quality of Life Questionnaire, breast cancer specific.

Table 4. Acute and Chronic Adverse Events

Source	Intervention/Comparisons	No. of Patients Evaluated	Acute and Chronic Adverse Events												Liver and/or Renal Biochemistry Alterations	
			First-Line Treatment: Single-Agent v Combination Regimens						Peripheral Neuropathy, Vomiting, Cardiomyopathy, Mucositis							
			Anemia	Neutropenia	Thrombocytopenia	Diarrhea	Fatigue	Alopecia	Infection	Nausea	Neuropathy	Vomiting	Cardiomyopathy	Mucositis		Skin Reactions
Stockler et al, 2011 (ANZBCTG trial) ⁵⁷	Intermittent capecitabine v Continuous capecitabine v CMF	107 107 109 (323)	P = ns P = ns 26%; P < .05	< 1% < 1%	P = ns P = ns	P = ns P = ns	P = ns P = ns	P = ns P = ns	P = ns P = ns	P = ns P = ns	P = ns P = ns	P = ns P = ns	Hand-foot syndrome: 14% 16% 0%; P < .05	—		
Lueck et al, 2013 (ASCO abstract) ⁴³	Paclitaxel or docetaxel + bevacizumab (B) v Paclitaxel or docetaxel + bevacizumab + capecitabine (BC)	202	—	—	*	—	—	—	—	—	—	—	—	Hand-foot syndrome* *All three: Gr3/4 more frequent with BC, P < .05	—	
Seidman et al, 2012 (SABCS abstract) ⁵³	NAB-paclitaxel 260 + bevacizumab 15 v NAB-paclitaxel 260 + bevacizumab 10 v NAB-paclitaxel 130 + bevacizumab 10	75 54 79 (208)	—	< 2% < 2% < 2%	—	—	39% 57% 39%; P < .05	—	—	—	—	33% 52% 44%; P = NR	—	—	—	
Seidman et al, 2011 ⁵⁴	Gemcitabine + docetaxel v Capecitabine + docetaxel	398	P = ns C: 5.2% 30.5; P < .001 .001 CD > G: 35.4%; P < .001	76.4%; GD > C: 5.2% 30.5; P < .001 .001 CD > G: 35.4%; P < .001	8% 0%; P < .001	P = ns P = ns	10.5% 5.3; P < .05	—	—	—	—	3.4% 8.0; P < .05	1.3% 4.4%; P < .05	1.3% 4.4%; P < .05	Hand-foot syndrome: 1.3% 4.4%; P < .05	—
Brufsky et al, 2011 ³⁴	Paclitaxel + bevacizumab v Paclitaxel + bevacizumab + gemcitabine	94 93 (187)	1.1% 4.3%; P = ns	25.5% 48.4%; P < .05	0% 2.2%; P = ns	0% 2.2%; P = ns	9.6% 14.0%; P = ns	0% 0%	2.1% 8.6%; P = ns	8.5% 0%	1.1% 1.1%; P = ns	0% 0%	0% 0%	0% 0%	—	—
Mavroudis et al, 2010 ⁴⁴	Docetaxel + eprubicin v Docetaxel + capecitabine	136 136 (272)	0.7% 0.7%; P = ns	57% 46%; P = ns	0.7% 0%; P = ns	0% 0%; P = ns	—	—	—	—	—	0% 0%; P = ns	0% 0%; P = ns	0% 4%; P < .05	Hand-foot syndrome: 0% 4%; P < .05	—
Yardley et al, 2012 (ASCO abstract) ⁶⁰	Paclitaxel + bevacizumab + everolimus v Placebo	55 57 (112)	P = ns P = ns	P = ns P = ns	P = ns P = ns	P = ns P = ns	—	—	—	—	—	—	13% 0%; P < .05	—	—	—

(continued on following page)

Table 4. Acute and Chronic Adverse Events (continued)

Source	Intervention/ Comparisons	No. of Patients Evaluated	Acute and Chronic Adverse Events											Liver and/or Renal Biochemistry Alterations			
			Anemia	Neutropenia	Thrombocytopenia	Diarrhea	Fatigue	Alopecia	Infection	Nausea	Neuropathy	Vomiting	Cardiomyopathy		Mucositis	Skin Reactions	
Second-Line Treatment: Single-Agent v Single-Agent Regimens																	
Schroder et al, 2011	Docetaxel (weekly) v (NTR1506) ⁸¹	79	—	6.3%	0	D/S: 3.8%	—	—	—	—	—	N/V: 2.6%	—	—	D/S: 3.8%	Hand-foot syndrome: 6.3%	—
	Docetaxel (every 3 weeks)	77	31.2%	1.3%	10.4%	—	—	—	—	—	—	N/V: 7.8%	—	—	10.4%	2.6%	—
Barrios et al, 2010 ⁶³	Sunitinib v Capecitabine	238	—	11%	8%	6%	7%	—	—	—	—	1%	—	—	3%	Hand-foot syndrome: 8%	—
	Capecitabine	240	< 4%	< 2%	< 2%	5%	1%	—	—	—	—	< 1%	—	—	< 2%	16%	—
Chan et al, 2005 ⁶⁶	Temsirolimus 75 v Temsirolimus 250	55	—	—	6%	—	—	—	—	—	—	—	—	—	6%	—	—
	Temsirolimus 250	51	—	—	4%	—	—	—	—	—	—	—	—	—	14%	—	—
Perez et al, 2004 ⁷⁸	Irinotecan weekly v Irinotecan every 3 weeks	52	—	29%	—	17%	6%	—	—	—	—	6%	—	—	—	—	—
	Irinotecan every 3 weeks	51	36%	—	—	12%	8%	—	—	—	—	16%	—	—	—	—	—
Bontenbal et al, 1998 ⁶⁴	Doxorubicin v Epirubicin	118	—	—	—	2.6%	—	74%	2.6%	—	—	N/V: 31%	—	—	—	—	—
	Epirubicin	114	—	—	—	—	—	—	—	—	—	26%	—	—	—	—	—
Nabholz et al, 1996 ⁷⁶	Paclitaxel 175 v Paclitaxel 135	235	4%	78%	3%	—	—	—	73%	3.5%	26%	N/V: 5%	7%	3%	3%	—	—
	Paclitaxel 135	236	2%	55%	2%	—	—	—	15%	5%	3%	5%	3%	4%	< 1%	—	—
Jones et al, 1995 ⁷¹	Vinorelbine v Melphalan	115	14%	—	0	0	—	0	—	—	4%	2%	3%	—	—	—	—
	Melphalan	64	34%	—	59%	2%	—	2%	—	—	5%	0	6%	—	—	—	—
Second-Line Treatment: Combination v Combination Regimens																	
Levy et al, 2005 ⁷³	Docetaxel + gemcitabine v Docetaxel + capecitabine	152	—	85%	—	8%	—	—	—	—	—	< 1%	—	—	4%	Hand-foot syndrome: < 1%	—
	Docetaxel + capecitabine	150	82%; P = ns	—	—	18%; P < .05	—	—	—	—	—	0%; P = ns	—	—	17% P < .05	26%; P < .05	—

NOTE: Dashes indicate not reported. Abbreviations: ANZBCTG, Australia & New Zealand Breast Cancer Trials Group; BSC, best supportive care; CMF, cyclophosphamide, methotrexate, fluorouracil;

of 34%³⁹ to a high of 88%,⁶⁰ with one outlier reporting none.⁴⁸ Because the focus of this guideline was on making recommendations for HER2-negative patients, the reported proportions of these patients approached 100%. None of the included studies reported on response rates from any previous treatment.

Details of the study characteristics of all 28 of the included second-line trials,^{6,31,39,61-85} including a total of 10,609 patients (minimum: 104⁷⁸; maximum: 1,221⁸³), can be found in the Data Supplement. The majority of trials included patients with ECOG PS 0 to 2 (or equivalent), although four trials^{31,80,82,84} only included patients with ECOG PS 0 to 1 (representing a healthier population), and one trial³⁹ included patients with ECOG PS 0 to 3 (representing a more at-risk population). Median ages in the trials ranged from a low of 47 years⁶⁹ to a high of 58.5 years,⁷⁴ with the majority of trials reporting median ages of approximately 55 years. Most of the trials reported proportions of premenopausal patients of approximately 35%, but this ranged from a low of 17.9%⁸⁵ to a high of 50%.⁷⁹ Patients reported as being either ER positive or PR positive ranged from a low of 22%⁷⁹ to a high of 100%.³¹ Because the focus of this guideline was on making recommendations for HER2-negative patients, the reported proportions of these patients approached 100%. Three^{61,77,82} of the included studies reported on response rates for previous treatments, with response ranging from a low of 45%⁸² to a high of 70%.⁶¹

Study Quality

Study quality was formally assessed for all 30³¹⁻⁶⁰ of the included first-line trials and for all 28^{6,31,39,61-85} of the included second-line trials, with details available in the Data Supplement. Design aspects related to the individual study quality were assessed by one reviewer and included factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, and so on. The risk of bias was assessed as low, intermediate, or high for most of the identified evidence. It was determined that this body of evidence represented trials of acceptable quality, and no exclusions were made on the basis of the assessment.

Efficacy Outcomes: First-Line Trials

Complete results for all outcomes of interest for all 30³¹⁻⁶⁰ first-line trials are reported in the Data Supplement, and significant results only are reported in Table 2. For OS or median survival, five trials reported significant differences (survival was a secondary outcome for all five trials), with results presented according to the comparison being made.

Endocrine therapy versus CT:

- There were no trials in this category for any of the end points we wished to study.

Single-agent versus single-agent, including dose and schedule:

- Gradishar et al, 2012³⁷ found NAB-paclitaxel 150 superior to NAB-paclitaxel 300, NAB-paclitaxel 100, or docetaxel alone (median survival, 33.8 months ν 27.2, 22.2, and 26.6 months, respectively; $P < .05$).

Single-agent versus combination regimens:

- Stockler et al, 2011⁵⁷ found capecitabine (given either intermittent or continuous) superior to CMF (median survival, 22 months ν 18 months, respectively; $P < .05$).

Combination versus combination regimens including dose and schedule:

- Robert et al, 2011⁵¹ found bevacizumab + paclitaxel superior to sunitinib + paclitaxel for 8-month survival (87% ν 79%, respectively; $P < .05$).
- O'Shaughnessy et al, 2011⁴⁸ found gemcitabine + carboplatin + iniparib superior to gemcitabine + carboplatin (median survival, 12.3 months ν 7.7 months, respectively; $P < .05$).
- Miles et al, 2010⁴⁵ found docetaxel + bevacizumab 15 superior to docetaxel + bevacizumab 7.5 and docetaxel + placebo for 1-year survival (84% ν 81%, 76%, respectively; $P < .05$).

For PFS, seven trials^{31,41,45,48,50-52} reported significant differences (PFS was a primary outcome for all but the trial reported by O'Shaughnessy et al⁴⁸).

Combination versus combination regimens:

- Lam et al, 2013⁴¹ found paclitaxel + bevacizumab + capecitabine \rightarrow bevacizumab + capecitabine superior to paclitaxel + bevacizumab \rightarrow capecitabine (11 months ν 8.4 months, respectively; $P < .05$).
- Baselga et al, 2012³¹ found capecitabine + sorafenib superior to capecitabine + placebo (7.6 month ν 4.1 months; $P < .05$).
- Rugo et al, 2012⁵² found paclitaxel with or without bevacizumab superior to ixabepilone with or without bevacizumab (10.4 months ν 7.6 months, respectively; $P < .05$).
- Robert et al, 2011⁵⁰ found capecitabine + bevacizumab superior to capecitabine + placebo (9.8 months ν 6.2; $P < .05$) and also found taxanes + anthracycline + bevacizumab superior to taxanes + anthracycline + placebo (10.7 months ν 8.3 months, respectively; $P < .05$).
- Robert et al, 2011⁵¹ found paclitaxel + bevacizumab superior to paclitaxel + sunitinib (9.2 months ν 7.4 months, respectively; $P < .05$).
- O'Shaughnessy et al, 2011⁴⁸ found gemcitabine + carboplatin + iniparib superior to gemcitabine + carboplatin (5.9 months ν 3.6 months, respectively; $P < .05$).
- Miles et al, 2010⁴⁵ found docetaxel + bevacizumab 15 superior to docetaxel + placebo alone (10.1 months ν 8.2 months, respectively; $P < .05$).

For overall response, three trials^{39,45,48} reported significant differences (overall response was a secondary outcome for all three trials).

Single-agent versus combination regimens:

- Katsumata et al, 2009³⁹ found docetaxel superior to doxorubicin + cyclophosphamide (40% ν 29%, respectively; $P < .05$).

Combination versus combination regimens:

- O'Shaughnessy et al, 2011⁴⁸ found gemcitabine + carboplatin + iniparib superior to gemcitabine + carboplatin (52% ν 32%, respectively; $P < .05$).
- Miles et al, 2010⁴⁵ found docetaxel + bevacizumab 15 superior to docetaxel + placebo (64.1% ν 46.4%, respectively; $P < .05$).

None of the trials reported differences on clinical benefit rates.

Efficacy Outcomes: Second-Line and Greater Trials

Complete results for all outcomes of interest for all 28^{6,31,39,61-85} second-line trials are reported in the Data Supplement, and significant results only are reported in Table 2.

For overall or median survival, seven^{6,62,67,71,77,79,83} trials reported significant differences (survival was a primary outcome for two^{62,83} trials), with results presented according to the comparison being made.

Single-agent versus single-agent:

- Jones et al, 1995⁷¹ found vinorelbine superior to melphalan for both median survival (35 weeks v 31 weeks, respectively; $P < .05$) and 1-year survival (35.7% v 21.7%, respectively; $P < .05$).

Single-agent versus combination regimens:

- Sparano et al, 2010⁸³ found ixabepilone + capecitabine superior to capecitabine alone for median survival (16.4 months v 15.6 months, respectively; $P < .05$).
- Albain et al, 2008⁶² found gemcitabine + paclitaxel superior to paclitaxel monotherapy in median survival (18.6 months v 15.8 months, respectively; $P < .05$).
- Reyno et al, 2004⁷⁹ found BMS-217380-01 + doxorubicin superior to doxorubicin alone in median survival (23.6 months v 15.6 months, respectively; $P < .05$).
- O'Shaughnessy et al, 2002⁶ found capecitabine + docetaxel superior to docetaxel alone in 1-year survival (57% v 47%, respectively; $P < .05$).
- Nabholz et al, 1999⁷⁷ found docetaxel alone superior to mitomycin + vinblastine for median survival (11.4 months v 8.7 months, respectively; $P < .05$).

Single-agent or combination regimen versus control, best supportive care (BSC), or observation:

- Cortes et al, 2011⁶⁷ found eribulin monotherapy superior to treatment of physician's choice in both median survival (13.1 months v 10.6 months, respectively; $P < .05$) and OS (46% v 42%; $P < .05$).

For PFS, five trials^{6,61,63,83} reported significant differences (PFS was a primary outcome for two^{31,83} trials).

Single-agent versus single-agent:

- Barrios et al, 2012⁶³ found capecitabine superior to sunitinib for median PFS (4.2 months v 2.8 months, respectively; $P < .05$).

Single-agent versus combination regimens:

- Sparano et al, 2010⁸³ found ixabepilone + capecitabine superior to capecitabine alone for median PFS (16.4 months v 15.6 months, respectively; $P < .05$).
- O'Shaughnessy et al, 2002⁶ found capecitabine + docetaxel superior to docetaxel alone in median PFS (6.1 months v 4.2 months, respectively; $P < .05$).

Single-agent or combination regimen versus control, BSC, or observation:

- Alba et al, 2010⁶¹ found pegylated liposomal doxorubicin superior to observation alone in TTP (8.4 months v 5.1 months, respectively; $P < .05$).

For ORR, six trials^{6,31,62,75,77,83} reported significant differences (ORR was not a primary outcome for any of the trials).

Single-agent versus combination regimens:

- Sparano et al, 2010⁸³ found ixabepilone + capecitabine superior to capecitabine alone for ORR (43.3% v 28.8%, respectively; $P < .05$).
- Albain et al, 2008⁶² found gemcitabine + paclitaxel superior to paclitaxel monotherapy for ORR (41.4% v 26.2%, respectively; $P < .05$).

- Miller et al, 2005⁷⁵ found capecitabine + bevacizumab superior to capecitabine for ORR (19.8% v 9.1%, respectively; $P < .05$).
- O'Shaughnessy et al, 2002⁶ found capecitabine + docetaxel superior to docetaxel alone for ORR (42% v 30%, respectively; $P < .05$).
- Nabholz et al, 1999⁷⁷ found docetaxel superior to mitomycin + vinblastine for ORR (30% v 11.6%, respectively; $P < .05$).

QoL Outcomes: First-Line Trials

Table 3 details results for QoL outcomes for the eight^{34-36,39,42,47,58,59} trials that reported significant differences (full QoL outcomes appear in the Data Supplement). Results are presented according to the comparison being made. Five trials^{34,36,47,58,59} reported significant differences.

Single-agent versus combination regimens:

- Cella et al, 2011³⁶ found paclitaxel + bevacizumab superior to paclitaxel 90 at 17 and 33 weeks (both P s $< .05$; Functional Assessment of Cancer Therapy-Breast Cancer Subscale).

Combination versus combination regimens:

- Svensson et al, 2012⁵⁹ found that global health scores, as well as physical functioning, role functioning, fatigue, pain, and appetite loss improvements were associated with longer survival times, but not PFS (all P s $< .05$; European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30 [EORTC-QLQ-C30]).
- Nuzzo et al, 2011⁴⁷ found a once every 3 weeks regimen of docetaxel + epirubicin or docetaxel + capecitabine superior to a weekly regimen in both global scores and role functioning (both $P < .05$; EORTC-QLQ-C30).
- Brufsky et al, 2011³⁴ found paclitaxel + bevacizumab superior to paclitaxel + bevacizumab + gemcitabine for global health scores, social and family well-being, and breast cancer additional concerns (all P s $< .05$; Functional Assessment of Cancer Therapy -Breast).
- Svensson et al, 2010⁵⁸ found epirubicin + paclitaxel + capecitabine superior to epirubicin + paclitaxel at baseline and at 9 months, but found epirubicin + paclitaxel superior for role functioning at 2 months but not at 9 months (all P s $< .05$; EORTC-QLQ-C30 and QLQ-BR23 [breast cancer specific]).

QoL Outcomes: Second-Line and Greater Trials

None of the second-line trials reported significant differences between treatment arms (see Data Supplement for full results).

AEs: First-Line Treatment

Table 4 details acute and chronic AEs (grades 3-4) for the 23^{31-34,37-40,42-48,50-54,56,57,60} first-line trials that reported on them (full results appear in Data Supplement). Results are presented according to the comparison being made. Seven^{34,43,44,53,54,57,60} of these trials reported significant differences:

Single-agent versus combination regimens:

- Stockler et al, 2011⁵⁷ found significantly higher neutropenia with CMF compared with either the intermittent or concurrent capecitabine arm (26% v $< 1\%$ v $< 1\%$, respectively; $P < .05$), but capecitabine was associated with significantly higher hand-foot syndrome (16% v 14% v 0%, respectively; $P < .05$).

Combination versus combination regimens including dose and scheduling:

- Lueck et al, 2013⁴³ found significantly higher thrombocytopenia, diarrhea, and hand-foot syndrome on the capecitabine containing arm (NR; $P < .05$).
- Seidman et al, 2012⁵³ found significantly higher fatigue associated with nab-paclitaxel 260 mg/m² + bevacizumab 10 mg/m² every 3 weeks compared with either nab-paclitaxel 260 mg/m² every 3 weeks + bevacizumab 15 mg/m² every 3 weeks or nab-paclitaxel 130 mg/m² weekly + bevacizumab 10 mg/m² every 2 weeks (57% v 39% v 39%, respectively; $P < .05$).
- Seidman et al, 2011⁵⁴ found significantly higher neutropenia (76.4% v 30.5%; $P < .05$), thrombocytopenia (8% v 0%; $P < .05$), and fatigue (10.5% v 6.3%; $P < .05$) associated with gemcitabine + docetaxel, but significantly higher nausea/vomiting (8% v 3.4%; $P < .05$), mucositis (4.4% v 1.3%; $P < .05$), and hand-foot syndrome (25.2% v 1.3%; $P < .05$) associated with capecitabine + docetaxel.
- Brufsky et al, 2011³⁴ found significantly higher neutropenia associated with paclitaxel + bevacizumab + gemcitabine compared with paclitaxel + bevacizumab (48.4% v 25.5%, respectively; $P < .05$).
- Mavroudis et al, 2010⁴⁴ found significantly higher hand-foot syndrome associated with docetaxel + capecitabine compared with docetaxel + epirubicin (4% v 0%, respectively; $P < .05$).

Single-agent or combination regimen versus control, BSC, or observation:

- Yardley et al, 2012⁶⁰ found significantly higher mucositis with paclitaxel + bevacizumab + everolimus compared with paclitaxel + bevacizumab + placebo (13% v 0%, respectively; $P < .05$).

In general, regimens that contained more drugs were associated with more frequent and more severe AEs compared with regimens that contained fewer drugs, and regimens that contained capecitabine were associated with more, and more severe, hand-foot syndrome.

AEs: Second-Line and Greater Treatment

Table 4 details acute and chronic AEs (grade 3-4) for the 26^{6,31-34,37-40,42-49,51-54,56,57,60-64,66-81,83-85} second-line trials that reported on them (full results appear in the Data Supplement). Results are presented according to the comparison made, with only one of the trials⁷³ reporting significant differences:

Combination versus combination regimens:

- Levy et al, 2005⁷³ found docetaxel + gemcitabine superior to docetaxel + capecitabine for diarrhea (8% v 18%, respectively; $P < .05$), mucositis (4% v 17%, respectively; $P < .05$), and hand-foot syndrome (<1% v 26%, respectively; $P < .05$).

In general, similarly to the first-line setting, regimens that contained more drugs were associated with more frequent and more severe AEs compared with regimens that contained fewer drugs, and regimens that contained capecitabine were associated with more, and more severe, hand-foot syndrome.

Results Summary

Table 5 provides a summary of the results, identifying the superior and inferior treatments for those trials that reported significant differences. These results are separated out by first-line treatment and second-line or greater treatment, and also by the comparison being made, either single-agent versus single agent, single-agent versus combination regimens, combination versus another combination, or single-agents or combinations versus BSC, observation alone, or another control.

Literature Review and Analysis

Question 1.

What are the indications for CT versus endocrine therapy in ER-positive first relapse metastatic breast cancer?

- Endocrine therapy, rather than CT, should be considered standard first-line treatment for patients with advanced breast cancer with ER/PR-positive disease. CT should be considered first in patients with severe symptoms or immediately life-threatening disease, for whom the likelihood of a CT response is higher and the time involved in an initial trial of endocrine therapy would be inappropriate.

Question 2.

Is there an optimal first-line CT and/or targeted therapy regimen for patients with HER2-negative advanced breast cancer?

- There is no single optimal first-line CT, and current evidence argues against the use of targeted therapy in combination with, or instead of, CT (except when there is immediately life-threatening disease).
 - What is the optimal timing, dose, schedule, and duration?*
 - Chemotherapy is generally best started once endocrine therapy is no longer effective. Optimal duration is hard to quantify; longer planned duration CT prolongs disease control compared with shorter but has to be balanced against progressive toxicity.
 - Is there evidence to prefer single-agent versus combination therapy?*
 - Yes, single-agent treatment provides equivalent efficacy with fewer AEs.
 - Should first-line treatment vary by hormone receptor status, tumor subtypes (eg, luminal A v luminal B v triple negative) or clinical characteristics of the patient or tumor(s) (eg, site[s] or extent of metastasis, prior treatment, performance status, and presence or absence of symptoms or immediately life-threatening disease)?*
 - Tumor type should not be used to dictate choice of first-line treatment. This should be based on efficacy, prior treatment, risk of life-threatening disease, relative toxicities, performance status, comorbid conditions, and patient choice.

Question 3.

Is there an optimal second- or greater-line CT and/or targeted therapy regimen?

- There is no single optimal second-line CT, and current evidence argues against the use of targeted therapy in combination with, or instead of, CT (except when there is immediately life-threatening disease).
 - What are the optimal timing, doses, schedules, and durations?*
 - CT is generally best started once endocrine therapy is no longer effective. Optimal duration is hard to quantify; longer

Table 5. Trial Results Summary

Study	Superior	Inferior	Outcome ($P < .05$)
First-Line Treatment			
Single-Agent v Single-Agent			
Gradishar et al, 2012 ³⁷	NAB-paclitaxel 150	NAB-paclitaxel 300, NAB-paclitaxel 100, docetaxel alone	Median survival
Single-Agent v Combination Regimens			
Stockler et al, 2011 ⁵⁷	Capecitabine (given either intermittently or continuously)	CMF	Median survival
	Capecitabine (given either intermittently or continuously)	CMF	Neutropenia
	CMF	Capecitabine (given either intermittent or continuous)	Hand-foot syndrome
Katsumata et al, 2009 ³⁹	Docetaxel	Doxorubicin + cyclophosphamide	ORR
Cella et al, 2011 ³⁶	Paclitaxel + bevacizumab	Paclitaxel 90	QoL
Combination v Combination Regimens			
Robert et al, 2011 ⁵¹	Bevacizumab + paclitaxel	Sunitinib + paclitaxel	Survival (at 8 months), PFS
O'Shaughnessy et al, 2011 ⁴⁸	Gemcitabine + carboplatin + iniparib	Gemcitabine + carboplatin	Median survival, PFS, ORR
Miles et al, 2010 ⁴⁵	Docetaxel + bevacizumab 15	Docetaxel + bevacizumab 7.5	1-year survival
		Docetaxel + placebo	1-year survival, PFS, ORR
Lam et al, 2013 ⁴¹	Paclitaxel + bevacizumab + capecitabine → bevacizumab + capecitabine	Paclitaxel + bevacizumab → capecitabine	PFS
Baselga et al, 2012 ³¹	Capecitabine + sorafenib	Capecitabine + placebo	PFS
Rugo et al, 2012 ⁵²	Paclitaxel with or without bevacizumab	Ixabepilone with or without bevacizumab	PFS
Robert et al, 2011 ⁵⁰	Capecitabine + bevacizumab	Capecitabine + PL	PFS
	Taxanes + anthracycline + bevacizumab	Taxanes + anthracycline + PL	PFS
Nuzzo et al, 2011 ⁴⁷	Docetaxel + epirubicin or docetaxel + capecitabine every 3 weeks	Docetaxel + epirubicin or docetaxel + capecitabine weekly	QoL
Brufsky et al, 2011 ³⁴	Paclitaxel + bevacizumab	Paclitaxel + bevacizumab + gemcitabine	QoL, AEs, neutropenia
Svensson et al, 2010 ⁵⁸	Epirubicin + paclitaxel + capecitabine	Epirubicin + paclitaxel	QoL, baseline, 9 months
	Epirubicin + paclitaxel	Epirubicin + paclitaxel + capecitabine	Role functioning, 2 months
Lueck et al, 2013 ⁴³	Paclitaxel or docetaxel + bevacizumab	Paclitaxel or docetaxel + bevacizumab + capecitabine	AEs (thrombocytopenia, diarrhea, hand-foot syndrome)
Seidman et al, 2012 ⁵³	NAB-paclitaxel 260 + bevacizumab 15	NAB-paclitaxel 260 + bevacizumab 10	AEs, fatigue
	NAB-paclitaxel 130 + bevacizumab 10	NAB-paclitaxel 260 + bevacizumab 10	AEs, fatigue
Seidman et al, 2011 ⁵⁴	Capecitabine + docetaxel	Gemcitabine + docetaxel	AEs, neutropenia, thrombocytopenia, fatigue
	Gemcitabine + docetaxel	Capecitabine + docetaxel	AEs, nausea/vomiting, mucositis, hand-foot syndrome
Mavroudis et al, 2010 ⁴⁴	Docetaxel + epirubicin	Docetaxel + capecitabine	AEs, hand-foot syndrome
Single-Agent or Combination Regimen v Control, BSC, or Observation			
Yardley et al, 2012 ⁶⁰	Placebo	Paclitaxel + bevacizumab + everolimus	AEs, mucositis
Second-Line Treatment			
Single-Agent v Single-Agent			
Jones et al, 1995 ⁷¹	Vinorelbine	Melphalan	Median survival 1-year survival
Barrios et al, 2012 ⁶³	Capecitabine	Sunitinib	Median PFS
Single-Agent v Combination Regimens			
Sparano et al, 2010 ⁸³	Ixabepilone + capecitabine	Capecitabine alone	Median survival, median PFS, ORR
Albain et al, 2008 ⁶²	Gemcitabine + paclitaxel	Paclitaxel monotherapy	Median survival, ORR
Reyno et al, 2004 ⁷⁹	BMS-217380-01 + doxorubicin	Doxorubicin	Median survival
Miller et al, 2005 ⁷⁵	Capecitabine + bevacizumab	Capecitabine	ORR
O'Shaughnessy et al, 2002 ⁶	Capecitabine + docetaxel	Docetaxel	Median survival, median PFS, ORR
Nabholtz et al, 1999 ⁷⁷	Docetaxel	Mitomycin + vinblastine	Median survival, ORR
		Combination v Combination Regimens	
Baselga et al, 2012 ³¹	Capecitabine + placebo	Capecitabine + sorafenib	PFS
Levy et al, 2005 ⁷³	Docetaxel + gemcitabine	Docetaxel + capecitabine	AEs, diarrhea, mucositis, hand-foot syndrome
Single-Agent or Combination Regimen v Control, BSC, or Observation			
Cortes et al, 2011 ⁶⁷	Eribulin monotherapy	Treatment of physician's choice	Median survival
Alba et al, 2010 ⁶¹	Pegylated liposomal doxorubicin	Observation alone	TTP

Abbreviations: AE, adverse event; BSC, best supportive care; CMF, cyclophosphamide, methotrexate, fluorouracil; ORR, overall response rate; PFS, progression-free survival; PL, placebo; QoL, quality of life; TTP, time to progression.

planned duration CT prolongs disease control compared with shorter but has to be balanced against progressive toxicity.

B. *Is there evidence to prefer single agent Versus combination therapy?*

- Yes, single-agent treatment provides equivalent efficacy With fewer adverse effects.

C. *Should treatment regimen vary by tumor subtypes or clinical characteristics?*

- Tumor type should not be used to dictate choice of first-line treatment. This should be based on efficacy, prior treatment, risk of life-threatening disease, relative toxicities, performance status, comorbid conditions, and patient choice.

Question 4.

At what point should anticancer therapy be discontinued? Is there evidence to prefer maintenance versus interrupted therapy?

- Later lines of CT should be based on response to prior lines, performance status, the likelihood of further benefit balanced against toxicity, and patient choice.

DISCUSSION

Although we found 79 studies that met the eligibility criteria for evidence informing these guideline recommendations, including 20 systematic reviews or meta-analyses, there are some limitations clinicians should be made aware of. For one, the selection of questions asked in these trials was arbitrary and not guided often enough by clinical need. For example, we have drawn conclusions on important questions including endocrine therapy versus CT as first-line treatment for ER-positive disease, and single-agent versus combination CT, but we feel that more randomized trial data on these key questions would be valuable. Likewise, there is a need for further randomized data that closely link efficacy with QoL. An important example is duration of CT. A meta-analysis¹⁸ has indicated that there is indeed a marginal improvement in OS and a substantial improvement in PFS for longer versus shorter planned duration of CT, but the challenge for the clinician, and indeed the patient, is the balance between treatment-related toxicity and tumor-related symptomatology. In addition, an important trial that clinicians would be aware of could not be included in the evidence review for this CPG as it was published in abstract form outside of the literature search dates (and has not yet been published in full). This was the negative phase III trial reported by O'Shaughnessy et al,⁸⁶ which was a follow-up to the positive phase II trial by the same authors,⁴⁸ which was included in this CPG as it was available in fully published form. Although the absence of this article does not affect our recommendations at all, its exclusion must be noted.

We have made the recommendation that treatment selection must involve not just efficacy data, but other factors including toxicity of treatment, performance status, comorbid conditions, and patient preference (eg, oral *v* intravenous CT, the risk of alopecia, etc). This is based on our overall conclusion that it is possible that there is an optimal schedule or duration of treatment that we have failed to establish simply because the appropriate trials have not been done. However, given the heterogeneity of breast cancer, even when restricted to HER2-negative disease, it is also possible that "one size will never fit all" and that there is no best treatment for most patients.

Finally our recommendation that targeted therapy has not so far been shown to enhance or replace CT in this large patient subgroup is likely to be short lived. With the speed of current developments in cancer genomics and the emergence of drugable targets, we anticipate a major role for these new approaches sooner rather than later.

RECOMMENDATIONS

The recommendations were developed on the basis of systematic reviews of the scientific literature and expert panel consensus, using the best available evidence and clinical experience as guides. The recommendations are evidence based and informed by RCT data. Summary descriptions of results are provided in the literature review and analysis section. Ratings for the type of recommendation and strength of the evidence are offered (see Methodology Supplement for rating definitions).

The guideline recommendations were crafted, in part, by using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software⁸⁷ (see Methodology Supplement). A guideline implementability review was conducted to improve clarity around recommended actions for clinical practice

SPECIAL COMMENTARY

The treatment of advanced breast cancer is an area of intense research, and data are evolving quite rapidly, which means that any recommendations are likely to change. While there have been improvements in survival over time for women with advanced disease, including those that are HER2 negative, more effective therapies are desperately needed as too many women are still dying of this disease. Thus, clinical trials are imperative as is attention to the palliation of symptoms, both medical and psychosocial, throughout the course of a patient's care to prevent undue suffering. Trials are needed to address the following gaps in knowledge:

1. Novel targeted therapies to enhance, or even to replace, CT
2. More intensive combination CT of oligometastases combined where appropriate with other modality (eg, radiotherapy or surgical excision *v* standard single agent)

PATIENT AND CLINICIAN COMMUNICATION

This section is based on 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 ASCO's 2009 stage IV non-small-cell lung cancer guideline⁸⁸ and to literature on risk communication for patients with cancer.⁸⁹ A patient who is newly diagnosed with metastatic disease versus one for whom first- and/or second- or greater-line treatment has failed to be effective is likely to face some different issues, although clinical teams are encouraged to discuss the option of clinical trials regardless. Clinicians should consider issues relevant to communicating with patients with metastatic breast cancer, including the

importance of evidence-based treatment, referring patients to Cancer.net and psychosocial support, and introducing concepts of concurrent palliative and antitumor therapy.^{88,90-92}

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 are members of racial/ethnic minorities suffer disproportionately from comorbid conditions, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.⁹³⁻⁹⁶ Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this CPG, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

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 multiple chronic conditions (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 whose study selection criteria 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 to make 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, highlighting the importance of shared decision making around guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of the above considerations, 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 MCC.

For female patients with breast cancer who are under 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 breast cancer patients who are over 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. Refer to the table in the Data Supplement for details on the number of patients affected by these comorbid conditions and other supplementary information.

COST IMPLICATIONS

Although many of the currently used CT drugs in this setting are off-patent, emerging targeted therapies will come with considerable cost implications for both insurers and patients. As much of the research in advanced breast cancer is focused on these novel targeted agents, costs will continue to rise.

EXTERNAL REVIEW

The draft CPG was distributed to three clinicians who were not members of the Expert Panel for review (see Acknowledgments). Main comments included: inclusion of several trials that were outside of the search dates for the systematic review, lack of availability of the targeted therapy agent in some areas, a request to change the language around the likelihood of finding an optimal therapy regimen that would address the needs of all patients, and other changes of an editorial nature. All comments were considered by the Working Group, and changes were made to address all the main comments.

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 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 through 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*.

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.

ADDITIONAL RESOURCES

More information, including Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and resources, is available at www.asco.org/guidelines/ABC_HER2-negative_chemo. Patient information is available there and at 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

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Manuscript writing: All authors

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Affiliations

Ann H. Partridge, Dana-Farber Cancer Institute; Steven E. Come, Beth Israel Deaconess Medical Center; Beverly Moy, Massachusetts General Hospital, Boston, MA; R. Bryan Rumble, American Society of Clinical Oncology, Alexandria; Michael A. Danso, Virginia Oncology Associates, Norfolk, VA; Lisa A. Carey, University of North Carolina, Chapel Hill, NC; Nancy E. Davidson, University of Pittsburgh Cancer Institute/University of Pittsburgh Medical Center, Pittsburgh, PA; Angelo Di Leo, Sandro Pitigliani Medical Oncology Unit, Prato, Italy; Julie Gralow, University of Washington/Seattle Cancer Care Alliance, Seattle, WA; Gabriel N. Hortobagyi, The University of Texas MD Anderson Cancer Center, Houston, TX; Douglas Yee, University of Minnesota/Masonic Cancer Center, Minneapolis, MN; Shelley B. Brundage, Patient Representative, Washington, DC; Maggie Wilcox, Independent Cancer Patients' Voice; and Ian E. Smith, Royal Marsden Hospital, London, United Kingdom.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**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**

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Ann Partridge

No relationship to disclose

R. Bryan Rumble

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Lisa Carey

Consulting or Advisory Role: AstraZeneca

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G1 Therapeutics Genentech GlaxoSmithKline Novartis

Research Funding: Genentech GlaxoSmithKline Sanofi

Steven Come

Consulting or Advisory Role: Genentech/Roche

Expert Testimony: Pfizer

Nancy Davidson

No relationship to disclose

Angelo Di Leo

Honoraria: Roche Novartis Pfizer AstraZeneca Genomic Health Eisai

Consulting or Advisory Role: Roche Novartis Pfizer AstraZeneca

Pierre Fabre

Travel, Accommodations, Expenses: Roche Novartis Pfizer AstraZeneca

Eisai

Julie Gralow

Research Funding: Roche/Genetech (Inst), Novartis (Inst), Amgen

(Inst)

Gabriel Hortobagyi

Consulting or Advisory Role: Pfizer Antigen Express Novartis Galena

Genentech Amgen AstraZeneca

Research Funding: Novartis (Inst)

Travel, Accommodations, Expenses: Novartis

Beverly Moy

No relationship to disclose

Douglas Yee

Consulting or Advisory Role: Symphogen Boehringer Ingelheim

Genentech/Roche

Shelley Brundage

No relationship to disclose

Michael Danso

Honoraria: Amgen

Maggie Wilcox

No relationship to disclose

Ian E. Smith

No relationship to disclose

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Appendix**Table A1.** Expert Panel Membership

Ann H. Partridge, MD (Co-chair)	Dana-Farber Cancer Institute, Boston, MA
Ian E. Smith, MD (Co-chair)	Royal Marsden Hospital, London , UK
Shelley B. Brundage	—
Lisa A. Carey, MD	University of North Carolina, Chapel Hill, NC
Steven E. Come, MD	Beth Israel Deaconess Medical Center, Boston, MA
Michael A. Danso, MD	Virginia Oncology Associates, Norfolk, VA
Nancy E. Davidson, MD	University of Pittsburgh Cancer Institute/University of Pittsburgh Medical Center, Pittsburgh, PA
Angelo Di Leo, MD	Sandro Pitigliani Medical Oncology Unit, Prato, Italy
Julie Gralow, MD	University of Washington/Seattle Cancer Care Alliance, Seattle, WA
Gabriel N. Hortobagyi, MD	University of Texas, MD Anderson Cancer Center, Houston, TX
Beverly Moy, MD	Massachusetts General Hospital, Boston , MA
R. Bryan Rumble, MSc	American Society of Clinical Oncology, Alexandria, VA
Maggie Wilcox	—
Douglas Yee, MD	University of Minnesota/Masonic Cancer Center, Minneapolis, MN