Fulvestrant for Systemic Therapy of Locally Advanced or Metastatic Breast Cancer in Postmenopausal Women: Guideline Recommendations

Members of the Breast Cancer Disease Site Group

Report Date: September 25, 2008

A review conducted in October 2013 put Evidence-based Series (EBS) 1-13 in the Education and Information section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol).

Evidence-based series (EBS) 1-13 consists of three sections:
Section 1: Guideline recommendations (ENDORSED [pending])
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process
Section 4: Document Review Summary and Review Tool

and is available on the CCO Web site (http://www.cancercare.on.ca)
PEBC Breast Cancer DSG page at:
http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/

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Guideline Report History

<table>
<thead>
<tr>
<th>GUIDELINE VERSION</th>
<th>SYSTEMATIC REVIEW</th>
<th>PUBLICATIONS</th>
<th>NOTES AND KEY CHANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 25, 2008</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table of Contents

Section 1: Guideline recommendations ................................................................. 1
Section 2: Evidentiary Base ..................................................................................... 9
Section 3: EBS Development Methods and External Review Process ....................... 36
Section 4: Document Review Summary and Review Tool .......................................... 43
Fulvestrant for Systemic Therapy of Locally Advanced or Metastatic Breast Cancer in Postmenopausal Women: Guideline Recommendations

J. Flemming, Y. Madarnas, J. Franek, and the Breast Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: September 25, 2008

SUMMARY

These guideline recommendations have been ARCHIVED, which means that the document will no longer be tracked or updated but may still be useful for academic or other informational purposes. Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2008 and 2013, and for details on how this Clinical Practice Guideline was ARCHIVED.

QUESTIONS

- Compared to tamoxifen and aromatase inhibitors, does fulvestrant improve outcomes for first-line therapy of locally advanced or metastatic breast cancer?
- Compared to aromatase inhibitors, does fulvestrant improve outcomes for second-line or later therapy of locally advanced or metastatic breast cancer?
- Compared to therapy alone, does fulvestrant in combination with other therapies improve outcomes?
- What is an appropriate dose and schedule of fulvestrant?
- Are there any factors that predict the outcomes of fulvestrant therapy?

TARGET POPULATION

Postmenopausal women with locally advanced or metastatic breast cancer

Section 1: RECOMMENDATIONS
RECOMMENDATIONS AND KEY EVIDENCE

1. **Patients with NO prior endocrine or cytotoxic therapy for advanced disease and NO recent adjuvant therapy (within previous twelve months)**

Fulvestrant is NOT recommended as an alternative to tamoxifen for first-line therapy of locally advanced or metastatic breast cancer in postmenopausal women who have had no prior endocrine or cytotoxic therapy for advanced disease and no recent adjuvant endocrine therapy (within previous twelve months).

- There has been one superiority, Phase III, multicentre, randomized controlled trial (RCT) by Howell et al. (1) comparing fulvestrant 250 mg intramuscularly (IM) q (every) monthly versus (vs.) tamoxifen 20 mg daily for first-line metastatic therapy of locally advanced or metastatic breast cancer in postmenopausal women (n=587). In this trial:
  - There were no significant differences between therapy arms with respect to time-to-progression (TTP; primary endpoint), tumour response to treatment, or quality of life (QOL). A prospectively planned subset analysis of patients with known estrogen-receptor-positive (ER+) and/or progesterone-receptor-positive (PgR+) tumours (~79% of population) similarly showed no significant difference for TTP.
  - When adjusted for baseline covariates, a significant benefit in overall survival (OS) in favour of tamoxifen was seen (38.7 vs. 36.5 months, HR 1.29, 95% confidence interval [CI] 1.01-1.64, p=0.04). An additional significant benefit for tamoxifen was identified for time-to-treatment-failure (TTF) under both adjusted (7.8 vs. 5.9 months, HR 1.24, 95% CI 1.03-1.50, p=0.026) and unadjusted analyses (HR 1.21, 95% CI 1.01-1.46, p=0.039). However, the advantage of tamoxifen in OS and TTF disappeared when analyzed among patients with ER+ and PgR+ tumours.
  - The superiority of fulvestrant was therefore not supported.
  - The above results were also not consistent with a predefined criterion for fulvestrant non-inferiority. However, an unplanned, exploratory analysis of TTP (primary endpoint) among patients with tumours ER+ and PgR+ was consistent with a predefined criterion for fulvestrant non-inferiority. Further, direct evidence is required to confirm such exploratory data.
  - Tolerability measures were similar between therapy arms although patients receiving tamoxifen experienced more hot flashes than those taking fulvestrant (24.7% vs. 17.7%, p=0.0501, tamoxifen vs. fulvestrant).

2. **Patients who have recurred on prior adjuvant endocrine therapy or have progressed on prior endocrine therapy for advanced disease**

Fulvestrant may be considered as alternative therapy to anastrozole for locally advanced or metastatic breast cancer in postmenopausal women with hormone-receptor-positive (ER+ and/or PgR+) breast cancer that has recurred on prior adjuvant tamoxifen therapy or progressed on prior tamoxifen therapy for advanced disease. Clinicians should be aware of the methodological concerns of the key evidentiary trials used in formulating this recommendation.

Factors that may influence the choice of fulvestrant versus anastrozole therapy include a slightly decreased, although still significant, incidence of joint disorders and the potential for improved compliance with fulvestrant.
• Two superiority, Phase III, multicentre RCTs (European Open-Label Trial 0020 [2]
  and U.S. Double-Blind Trial 0021 [3]) compared fulvestrant 250 mg IM q monthly to
  anastrozole 1 mg daily in patients who had received prior adjuvant tamoxifen
  therapy, or tamoxifen for advanced disease. Combined analyses (n=851) of these
two trials across multiple reports (4-11) have found:
  o No significant difference between groups for TTP (primary endpoint), TTF,
    objective response rate (ORR), clinical benefit rate (CBR; the sum of complete
    response + partial response + stable disease), and OS.
  o Superiority of fulvestrant was therefore not supported (4).
  o Additional retrospective analysis of the combined data found no significant
    differences between therapy arms with respect to ORR or CB across
    subpopulations of patients with or without visceral metastases (11).
  o Unplanned, retrospective analyses of the combined data, based on a United
    States regulatory submissions criterion for hormonal treatments that the upper
    one-sided confidence limit of the hazard ratio (HR) for the primary endpoint
    of TTP not be greater than 1.25 (i.e., the margin of difference), concluded non-
    inferiority of fulvestrant to anastrozole (5.5 vs. 4.1 months, HR 0.95, 95% CI
    0.82-1.10). The secondary endpoint of ORR also confirmed non-inferiority (4).
  o In favour of fulvestrant, duration of response (DOR) was significantly longer for
    fulvestrant vs. anastrozole when analyzed for all randomized patients (ratio of
    average response durations = 1.30, p<0.01), or just for responders (16.7 vs.
    13.7 months; p-value not reported) (5).
  o 18.4% of patients in the combined population were ER/PgR unknown or ER/PgR-
    negative, but analyses were not stratified by hormone-receptor status (4).
  o Tolerability was similar between therapy arms, with the exception of a higher
    incidence of joint disorders for those taking anastrozole (8.3% vs. 12.8%,
    p=0.0234, fulvestrant vs. anastrozole, respectively) (4).

Qualifying Statements
• The U.S. Double-Blind Trial 0021 used a double-dummy, double-blinding approach
  whereby patients were given both placebo and actual therapy simultaneously, whereas
  the European Open-Label Trial 0020 did not blind patients or investigators to therapy
  (4).
• There is concern about the methodological rigour of Trials 0020/0021 in concluding
  fulvestrant non-inferiority as these trials were originally designed for detecting
  superiority. There is additional concern about whether proper statistical adjustments
  were made to account for multiple interim analyses in subsequent reports of these
  trials (6-11) (original trial reports indicated proper adjustments [4,5]). These
  concerns are fully discussed in Section 2: Evidentiary Base below. The Breast Cancer
  Disease Site Group (DSG) holds the view that these concerns, while important, are
  insufficient to invalidate the recommendations provided above.
• Fulvestrant has not been thoroughly examined in patients with tumours ER- and/or
  PgR-. While those RCTs identified in Recommendations #1 and #2 above included
  patients with tumours ER- and/or PgR-, an overwhelming majority of patients had ER+
  and/or PgR+ breast cancer: 79.2% in the trial by Howell et al. (1) and 81.6% in the
  combined Trials 0020 and 0021 (4). Furthermore, subgroup analyses based on
  hormone-receptor status were not consistently evaluated. Lastly, as fulvestrant is an
  ER-antagonist, it is the view of the authors of this report to maintain the use of
  fulvestrant in patients with ER/PgR receptor-positive breast cancer pending any direct

Section 1: RECOMMENDATIONS
evidence that may suggest its use in hormone receptor-negative patients is acceptable and efficacious.

**Fulvestrant may be considered as alternative therapy to exemestane for locally advanced or metastatic breast cancer in postmenopausal women with hormone-receptor-positive (ER+ and/or PgR+) breast cancer that has recurred on prior adjuvant nonsteroidal aromatase inhibitor (NSAI) therapy (during or within six months of discontinuation) or progressed on prior NSAI therapy for advanced disease.**

**Factors that influence the choice of fulvestrant versus exemestane therapy include the potential for improved compliance in favour of fulvestrant.**

- The Evaluation of Faslodex vs. Exemestane Clinical Trial (EFECT) is a superiority Phase III, multicentre, double-blind, double-dummy RCT by Chia et al. (12) comparing a fulvestrant loading-dose regimen (500 mg IM day 0, 250 mg IM on days 14 and 28, and 250 mg IM injection q monthly thereafter) with exemestane 25 mg orally [po] daily in women with HR+ breast cancer that has recurred or progressed on prior NSAI therapy. At the time of a planned final analysis (median follow-up 13 months; n=693):
  - The median TTP (primary endpoint) in both groups was 3.7 months (HR 0.93, 95% CI 0.819-1.133, p=0.65). Adjusting for covariates made little difference (HR 0.968, 95% CI 0.822-1.141).
  - The ORR (7.4% vs. 6.7%, OR 1.12, 95% CI 0.578-2.186, p=0.736) and CBR (32.2% vs. 31.5%, OR 1.03, 95% CI 0.72-1.487, p=0.853) did not differ significantly between fulvestrant and exemestane treatment groups respectively. The median DOR, measured from the date of random assignment was 13.5 vs. 9.8 months (n=38), and 7.5 vs. 5.5 months when measured from date of first response in favour of fulvestrant (p-values not reported) (12).
  - According to an abstract at the 2007 San Antonio Breast Cancer Symposium (SABCS), median OS was not significantly different between treatment arms (24.3 vs. 23.1 months, HR 1.012, 95% CI 0.833-1.229, p=0.9072 in favour of fulvestrant) at a median follow-up of 20.9 months (13).
  - Both fulvestrant and exemestane were well tolerated with no significant differences in the incidence of adverse events. Quality of Life was measured with the Functional Assessment of Cancer Therapy-Endocrine Symptom (FACT-ES) and Trial Outcome Index (TOI) instruments. The mean difference between therapy arms across both QOL instruments was not significant (12).

**Qualifying Statements**

- Only 10% of women enrolled received their previous AI as adjuvant therapy, thus limiting the generalizability of results for this population (12).
- Roughly 60% of women received ≥2 endocrine therapies prior to trial therapy (13), and in roughly 60% of women, fulvestrant or exemestane was administered as third-line or later therapy (12). Thus, it is unclear as to the optimal sequencing and timing of fulvestrant administration (e.g., second-line, third-line) to derive utmost efficacy benefit, at least in comparison to exemestane.
- The EFECT trial authors further indicate that a possible misclassification of patients as AI-sensitive by treating oncologists at the time of prior NSAI therapy could have contributed to a lowered clinical efficacy and may have undermined the power of the study. To this point, an unplanned retrospective analysis looking at TTP in patients who received fulvestrant or exemestane as second-line treatment and were deemed
sensitive to the prior nonsteroidal AI concluded in favour of fulvestrant, albeit nonsignificantly (results not shown) (12).

- At the time of the first planned analysis, median survival, a planned endpoint for analysis, had not yet been reached (12) and was thus reported in a subsequent abstract at the 2007 SABCS (13).

3. **Recommended dosage**

| The recommended dose of fulvestrant for the treatment of locally advanced or metastatic breast cancer is 250 mg IM every month OR a loading dose schedule of 500 mg IM day 0, 250 mg IM on days 14 and 28, and 250 mg IM injection q monthly thereafter. |

Factors that may influence the choice of a loading dose include a shortened time to reach steady state (within one month vs. three to six months for standard dosage) although this may require further verification.

- In two Phase III trials comparing fulvestrant vs. anastrozole (Trial 0020 [2] and Trial 0021 [3], respectively), fulvestrant was administered at 250 mg IM q monthly (28 +/- 3 days) as either two separate 2.5 ml injections (2) or as a single 5 ml injection (3). The latter approach was also used in the study by Howell et al. (1).
- A randomized pharmacokinetic study (14) and a pharmacokinetic analysis of Trial 0020 and Trial 0021 (15), both comparing a single 5 ml injection with two separate 2.5 ml injections for the delivery of a 250 mg fulvestrant dose, found no difference in pharmacokinetics or tolerability.
- In a Phase III trial comparing fulvestrant to exemestane (EFECT Trial [12]), a loading dose schedule of fulvestrant was used (500 mg on day 0, 250 mg on day 14, 250 mg on day 28, and every 28 days thereafter). There are several currently active Phase III trials that are using this fulvestrant loading dose schedule (Southwest Oncology Group [SWOG]-S0226, Fulvestrant and Anastrozole Clinical Trial [FACT], Study of Faslodex, Exemestane and Arimidex [SOFEA]; Section 2: Table 5).
- Some data are available for indirect comparison between a standard and loading dose schedule. A pharmacokinetic study has shown that dosing with a single monthly injection of fulvestrant at the standard dosage of 250 mg IM can take three to six doses (hence three to six months) to reach steady state levels in the plasma (16). Original trial reports from the EFECT trial (12), as well as a more detailed abstract presented at the SABCS 2007 conference, indicate that a loading dose schedule allowed fulvestrant to reach steady state within only one month (28 days) of administration (17).
- No prospective trials have directly compared single monthly vs. loading dose schedules, but a retrospective analysis suggests similarity in response rate and duration of response (18).

4. **Combination Fulvestrant**

At present there are no published studies to guide a recommendation regarding the use of fulvestrant in combination with other chemotherapies for first-line or greater treatment of locally advanced or metastatic breast cancer. There are currently two active, ongoing Phase III trials (SWOG-S0226, FACT; Section 2: Table 5) comparing anastrozole vs. anastrozole plus simultaneous fulvestrant for first-line therapy of metastatic breast cancer. In addition, a third, ongoing Phase III trial (Cancer and Leukemia Group B [CALGB]-40302) is examining the use of second-line fulvestrant alone in comparison with the combination of

Section 1: RECOMMENDATIONS
fulvestrant plus lapatinib ditosylate, an epidermal growth factor receptor (EGFR) inhibitor, in HER2/neu-positive women (Table 5).

5. **Predictive factors of outcome on Fulvestrant therapy**
   
   There is insufficient evidence to guide a definitive recommendation regarding the interpretation of factors to predict an outcome for postmenopausal women undergoing fulvestrant therapy for locally advanced or metastatic breast cancer.

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For information about the PEBC and the most current version of all reports, please visit the CCO website at [http://www.cancercare.on.ca/](http://www.cancercare.on.ca/) or contact the PEBC office at:

Phone: 905-527-4322 ext. 42822    Fax: 905-526-6775    E-mail: ccopgi@mcmaster.ca
REFERENCES


7. Jones SE, Pippen J, Webster A. A retrospective analysis of the proportion of patients responding for 1, 1.5 and 2 years in two phase III studies of fulvestrant vs anastrozole [A6047]. Breast Cancer Res Treat. 2004;100 Suppl 1:S236.


Evidence-based Series 1-13: Section 2 (ARCHIVED 2013)

Fulvestrant for Systemic Therapy of Advanced or Metastatic Breast Cancer in Postmenopausal Women: Evidentiary Base

J. Flemming, Y. Madarnas, J. Franek, and the Breast Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: September 25, 2008

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QUESTIONS

- Compared to tamoxifen and aromatase inhibitors, does fulvestrant improve outcomes for first-line therapy of locally advanced or metastatic breast cancer?
- Compared to aromatase inhibitors, does fulvestrant improve outcomes for second-line or greater therapy of locally advanced or metastatic breast cancer?
- Does fulvestrant in combination with other therapies improve outcomes?
- What is an appropriate dose and schedule of fulvestrant?
- Are there any factors that predict the outcomes of fulvestrant therapy?

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among Canadian women and projections in 2007 alone estimated 5,400 deaths (1). Despite numerous advances in the diagnosis and treatment of early-stage breast cancer, many women develop metastatic
disease, and thus, treatment options directed at this population are currently the focus of active research.

Historically, tamoxifen has been the standard first-line therapy for estrogen receptor (ER) positive metastatic breast cancer. Tamoxifen is a selective ER-modulator (SERM) that acts primarily as an antagonist, binding to the ER, thereby preventing the subsequent binding of estrogen. However, tamoxifen also displays some estrogen agonist effects that are thought to be partially responsible for treatment failures (2). Third generation selective aromatase inhibitors (AI) anastrozole, letrozole, and exemestane are now available. These agents work by preventing the conversion of androgens to estrogen in fat, muscle, breast, and brain (3). Initially these agents were found to be effective in patients who had progressed after tamoxifen therapy (4-9) and more recently, third generation AIs have proved to be as effective as tamoxifen for first-line therapy in metastatic breast cancer (10-16). Unfortunately, progression of disease continues in some patients despite various intensive hormonal therapies indicating the need for other treatment options.

Fulvestrant (Faslodex®) is a unique ER antagonist that down-regulates the ER and abolishes estrogen-sensitive gene transcription. Fulvestrant has no known estrogen agonist effect indicating potential favourability over tamoxifen (17). Because of its unique mode of activity, fulvestrant has been studied as both first- and second-line therapy for locally advanced and metastatic breast cancer. The purpose of this systematic review is to evaluate the current evidence available and provide recommendations for clinicians regarding the use of fulvestrant as first-line or later treatment of locally advanced or metastatic breast cancer in postmenopausal women.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario’s Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle1. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by one clinician (JFlemming) and one methodologist (JFranek).

This systematic review is a convenient and up-to-date source of the best available evidence on the use of fulvestrant in locally advanced or metastatic breast cancer. The body of evidence in this review is primarily comprised of mature randomized controlled data from phase III trials. That evidence forms the basis of an EBS developed by the Breast Cancer Disease Site Group (DSG) (publication pending). The systematic review and companion guideline recommendations are intended to promote evidence-based clinical practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

MEDLINE (January 1996 to June 2008) and EMBASE (January 1996 to April 2008), databases and the Cochrane Central Register of Controlled Trials (CENTRAL) and Systematic Reviews (up to 1st Quarter 2008) were searched in their entirety for the dates indicated. A comprehensive search strategy was used that combined disease-specific (e.g., Breast Neoplasms in MEDLINE or Breast Tumor in EMBASE), treatment-specific (e.g., fulvestrant, Faslodex, or ICI 182,780), and publication-type-specific (e.g. randomized controlled trial) search terms. The combined search strategy, available in Appendix A, was applied simultaneously to MEDLINE, EMBASE, and CENTRAL and thus included all relevant subject and

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EMTREE headings, text words, and publication types. The Cochrane Library of Systematic Reviews was also searched using simply treatment-specific terms.

On-line conference proceedings from the American Society of Clinical Oncology (ASCO) (http://www.asco.org/; up to 2007) and the San Antonio Breast Cancer Symposium (SABCS) (http://www.sabcs.org/; up to 2007) were also searched in their entirety for relevant abstracts or presentations using a similar to that identified above. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearing House (http://www.guideline.gov/) were searched for existing evidence-based practice guidelines. Ongoing trials were identified through the U.S. National Institute's of Health (NIH) ClinicalTrials.gov and Cancer.gov databases.

All relevant articles and abstracts were selected and reviewed, and the reference lists from these sources were hand searched for additional trials.

Study Selection Criteria

**Inclusion Criteria**

- Fulvestrant alone or in combination with other systemic agents was evaluated in postmenopausal women with locally advanced or metastatic breast cancer.
- Publication types were randomized Phase II or III trials, clinical practice guidelines, or systematic reviews and/or meta-analyses of randomized trials.
- Locally advanced breast cancers were defined as Stage IIIB or greater.
- Reported outcomes included at least one of the following types of data: time to progression (TTP), time to treatment failure (TTF), objective or complete response rate, progression-free survival, overall survival (OS), compliance/continuation data, and toxicities.
- Clinical trial results were published as peer-reviewed journal articles or publicly available conference abstracts or presentations.

**Exclusion Criteria**

- Trials that were published in a language other than English, as translation capabilities were not available.
- Trials that had not yet reported on evaluable efficacy data and were ongoing at the time of literature searching.

Quality Appraisal of Evidence-Based Guidelines

The Appraisal of Guideline Research and Evaluation (AGREE) tool (18) was used by three independent methodologists (JFranek and others) and one clinician (JFlemming) to evaluate the quality of identified evidence-based guidelines. While all scoring domains of the AGREE tool were considered in the evaluation of guidelines, the Rigour of Development domain, describing the rigour of systematic methods in identifying and evaluating evidence, along with the Overall Rating, were considered to be most relevant in application for this systematic review.

Synthesizing the Evidence

Because of the small number of randomized controlled trials (RCTs) with comparable outcomes, and the fact that two relevant Phase III trials were already evaluated in a combined analysis, no statistical pooling of trial results was conducted.

RESULTS

Literature Search Results
Two evidence-based practice guidelines were identified through electronic searches (19,20) and one by reference checking (21). No systematic reviews were identified. Four relevant Phase III trials, described across twelve citations (22-33), met the above-stated inclusion criteria. Ten abstract citations were not included as they reported redundant or inutile data (34-43); six of these eleven abstracts were identified by hand searching (35-39,41). In addition, two retrospective reviews examining sensitivity to further endocrine therapy following progression on fulvestrant were excluded as they did not evaluate endpoints identified as important for this review (44,45). No randomized Phase II trials were identified. Seven of the twelve included citations describe various combined (meta)analyses using data from two of the identified Phase III trials (European Open-Label Trial 0020 and U.S. Double-Blind Trial 0021) (22,27,28,30-33). A flow diagram outlining the results from the search strategy is provided in Appendix B. The most updated and complete citations were used when describing and evaluating trial results.

Evidence-Based Guidelines and Recommendation Summary

All evidence-based guidelines were evaluated using the AGREE tool as described in the Methods. The quality of guidelines was modest, with AGREE scores for the Rigour of Development domain ranging from 36.9% to 65.5% (see Appendix C for complete evaluation). The reviewers did not recommend any guidelines for adoption, for the following reasons: fulvestrant therapy was only a minor topic of review across guidelines, which focused more globally on the treatment of metastatic breast cancer; the evidence base for metastatic fulvestrant was far less complete across guidelines than the available evidence identified from the search for this systematic review, with subsequent analyses and trials being available and not consistently evaluated across guidelines; and lastly, the reviewed guidelines addressed only single questions regarding the efficacy of fulvestrant and did not evaluate across those series of questions identified as important for this review. For these reasons, recommendations from the clinical practice guidelines were not adopted and did not influence any recommendations or conclusions produced through this systematic review.

Randomized Controlled Trials

Trial methodology and patient characteristics of the randomized trials identified for inclusion are summarized in Table 1. Trial design and quality issues are summarized in Table 2. Three of four trials used a double-dummy, double-blinding approach whereby patients were given both placebo and actual therapy simultaneously (23,26,29). Only one trial, the European Open-Label Trial 0020, did not blind patients or investigators to therapy (25). The method of randomization was poorly reported across trials. Three of four trials reported power and sample size calculations with all achieving their target sample size (25,26,29). These three trials reported that analyses of primary endpoints were conducted according to intention-to-treat (ITT) principles with two of the three trials, the European Open-Label Trial 0020 and the U.S. Double-Blind Trial 0021, reporting a correction factor for preliminary or interim analyses, but only in original reports of the individual studies (25,29) and in original reports of the combined data (27,32).

Multiple Reporting

As previously identified in the Literature Search Results above, multiple reports and analyses have been produced for single studies, particularly in respect to the combined data from the European Open-Label Trial 0020 and U.S. Double-Blind Trial 0021, arguably the two most influential studies conducted on fulvestrant to date. While original trial reports (25,27,29,32) indicated proper adjustments of statistical significance levels for the outcomes of TTP and ORR to account for multiple interim analyses, it is unclear whether proper
statistical adjustments were made in subsequent trial reports (22, 28, 30, 31, 33), and whether these analyses were planned or unplanned. This is an important issue as the probability of obtaining a significant result increases with the number of analyses being performed. Though the results from original trial reports are in concordance with subsequent efficacy analyses, readers are cautioned about the true level of statistical significance (p-value) obtained from subsequent trial reports and may want to refer to original trial results for additional verification. To this end, it should be noted that subsequent trial data are reported in place of original trial data—where appropriate, in this paper—to provide readers with the most up-to-date data.
Table 1. Phase III trials evaluating fulvestrant for locally advanced or metastatic breast cancer in postmenopausal women.

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<tr>
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<th>Treatment Arms</th>
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<td>Fulvestrant</td>
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<td>Double-blind, Double-dummy,</td>
<td>NR</td>
<td>Locally advanced or metastatic who progressed during adjuvant or first-line endocrine</td>
<td>bilateral oophorectomy</td>
</tr>
<tr>
<td>U.S. Double-Blind Trial 0021</td>
<td>Anastrozole</td>
<td>194</td>
<td>Multicentre, Phase III</td>
<td></td>
<td>therapy; prior sensitivity to hormone therapy or known ER or PgR positivity</td>
<td></td>
</tr>
<tr>
<td>Gradishar et al. (23)</td>
<td>Fulvestrant</td>
<td>351</td>
<td>Double-blind, Double-dummy,</td>
<td>2003 to 2005</td>
<td>Locally advanced or metastatic; hormone-receptor positive; prior progression on NSAI</td>
<td>Age ≥60 yrs, or age ≥45 yrs with amenorrhea for &gt;12 months or follicle stimulating</td>
</tr>
<tr>
<td>EFECT Trial</td>
<td>Exemestane</td>
<td>342</td>
<td>Multicentre, Phase III</td>
<td></td>
<td>therapy for advanced disease or recurrence on NSAI during adjuvant therapy or within six</td>
<td>hormone levels within postmenopausal range, or prior bilateral oophorectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>months of adjuvant therapy discontinuation</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ER, estrogen receptor; NR, not reported; NSAI, nonsteroidal aromatase inhibitor; PgR, progesterone receptor; yrs, years.
Table 2. Phase III trials evaluating fulvestrant for locally advanced or metastatic breast cancer in postmenopausal women - trial design and quality issues.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Blinding</th>
<th>Method of Randomization</th>
<th>Primary (Secondary) Endpoint</th>
<th>Expected Effect, Power, Planned Sample Size</th>
<th>Achieved Sample Size</th>
<th>ITT Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howell et al. (26)</td>
<td>Double-blind, all pts given both treatment and placebo (i.e. double-dummy)</td>
<td>Software-generated random assignment, separate for each centre</td>
<td>TTP (ORR, CBR, DOR, TTF, TTD)</td>
<td>TTP HR of fulvestrant compared to tamoxifen of ≥ 1.39 or ≤ 0.72, 80% power, 510 pts and 350 events required</td>
<td>Yes</td>
<td>Yes, with right censoring of pts that had not experienced event at time of TTP analysis</td>
</tr>
<tr>
<td>Howell et al. (25)</td>
<td>Open, non-blinded</td>
<td>NR</td>
<td>TTP</td>
<td>TTP HR of fulvestrant compared to anastrozole of ≥ 1.43 or ≤ 0.70, 90% power, 392 pts and 340 events required</td>
<td>Yes</td>
<td>Yes, with right censoring of pts that had not experienced event at time of TTP analysis</td>
</tr>
<tr>
<td>European Open-Label Trial 0020</td>
<td></td>
<td>NR</td>
<td>TTP</td>
<td>TTP HR of fulvestrant compared to anastrozole of ≥ 1.43 or ≤ 0.70, 90% power, 392 pts and 340 events required</td>
<td>Yes</td>
<td>Yes, with right censoring of pts that had not experienced event at time of TTP analysis</td>
</tr>
<tr>
<td>Osborne et al. (29) U.S. Double-Blind Trial 0021</td>
<td>Double-blind, all pts given both treatment and placebo (i.e. double-dummy)</td>
<td>NR</td>
<td>TTP</td>
<td>TTP HR of fulvestrant compared to exemestane of ≥ 1.31 or ≤ 0.76, 90% power, 600 pts and 580 events required</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gradishar et al. (23) EFECT Trial</td>
<td>Double-blind, all pts given both treatment and placebo (i.e. double-dummy)</td>
<td>NR</td>
<td>TTP (OS, ORR, CBR, DOR, and tolerability)</td>
<td>TTP HR of fulvestrant compared to exemestane of ≥ 1.31 or ≤ 0.76, 90% power, 600 pts and 580 events required</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: CBR, clinical benefit rate; DOR, duration of response; HR, hazard ratio; ITT, intention-to-treat analysis; NA, not applicable; NR, not reported; ORR, objective response rate; OS, overall survival; pts, patients; TTD, time-to-death; TTF, time-to-treatment-failure; TTP, time-to-progression
Measures and Outcomes

Patients with No Prior Metastatic or No Recent Adjuvant Endocrine Therapy

One Phase III trial (26) explored the use of fulvestrant in patients with no prior metastatic therapy and no recent adjuvant endocrine therapy (within previous twelve months).

Fulvestrant versus Tamoxifen

One superiority, Phase II, multicentre, RCT (26), reported by Howell et al. in 2004, compared tamoxifen 20 mg orally once daily versus (vs.) fulvestrant 250 mg as an intramuscular injection (IM) monthly (28 ± 3 days) with no loading schedule. Patient and trial characteristics are described in Tables 1 and 2, and efficacy and toxicity measures in Tables 3 and 4 respectively. Patients were considered eligible if they had received no prior endocrine or cytotoxic chemotherapy for advanced disease, or had received no adjuvant endocrine therapy within twelve months before trial entry. At a median follow-up of 14.5 months there were no significant differences seen for time to progression (TTP; primary endpoint), tumour response to treatment, quality of life (QOL), or tolerability. Superiority of fulvestrant was therefore not supported. Furthermore, according to a predefined non-inferiority criterion of the upper 95% confidence interval (CI) of hazard ratio (HR) ≤ 1.25, non-inferiority of fulvestrant could not be confirmed for the primary endpoint of TTP. Further analysis revealed a statistically significant advantage in overall survival (OS) in actual favour of tamoxifen when unadjusted for preplanned baseline covariates. Additional significant improvement with tamoxifen was seen for TTF, under both adjusted and unadjusted analysis, and for clinical benefit (CB; the sum of complete response + partial response + stable disease). However, these advantages disappeared when analyses were carried out for patients only with ER+ and/or PgR+ tumours (OS, 39.3 vs. 40.7 months, p=0.30; TTF, 7.5 vs. 8.0 months, p=0.19; and CB, 62.7 vs. 57.1%, p=0.22; for tamoxifen vs. fulvestrant). Of the total patients, 77.4% and 78.9% had ER+ and/or PgR+ tumours for tamoxifen or fulvestrant therapy arms, respectively.

An unplanned, exploratory analysis of TTP in patients with tumours both ER+ and PgR+ (42% of patient population) was consistent with non-inferiority (HR 0.85, 95% CI 0.63 to 1.15; p=0.031). However, further, direct evidence is needed to confirm such exploratory data.

Statistical analysis of prospectively defined adverse events revealed no significant difference between therapy arms although a higher incidence of hot flashes amongst patients receiving tamoxifen approached statistical significance (p=0.0501, tamoxifen vs. fulvestrant; see Table 4).

Fulvestrant versus Other First-Line Endocrine Therapies

There are no reported trials of fulvestrant vs. anastrozole, letrozole, or exemestane for the target patient population.

Patients with Prior Metastatic or Adjuvant Endocrine Therapy

Three Phase III trials, described across eleven citations (22-25,27-33), investigated the use of fulvestrant in patients who had tumour progression on prior endocrine therapy for metastatic disease or recurrence on adjuvant endocrine therapy. Details of these trials are described in the text below. Efficacy results are summarized in Table 3 and toxicities in Table 4.

Fulvestrant versus Anastrozole

There have been two superiority, Phase III, multicentre RCTs (European Open-Label Trial 0020 and U.S. Double Blind Trial 0021) comparing fulvestrant vs. anastrozole for second-
line therapy (Trial 0020 (25); Trial 0021 (29)). Because of the similarities between the two trials, several combined (meta)analyses have been reported (22,27,28,30-33). Both trials recruited similar patient populations, and the patient and trial characteristics are summarized in Tables 1 and 2. In both trials, patients were randomized to receive either fulvestrant 250 mg IM every month (1 x 5 ml in Trial 0020, and 2 x 2.5 ml in Trial 0021) with no loading schedule, or anastrozole 1 mg orally, daily. Roughly 96.5% of the combined patient population had tumour progression on tamoxifen therapy for advanced disease or recurrence on adjuvant tamoxifen therapy. Results of the most recent combined analysis are provided in place of older, individual trial reports.

No significant differences were observed between the fulvestrant and anastrozole therapy arms for TTP (primary endpoint), objective response rate (ORR), TTF, CB, and OS (median follow-up ranging from 15.1 to 27.0 months; see Table 3). Superiority of fulvestrant was therefore not supported. Furthermore, a pair of retrospective analyses indicated no significant difference between therapy arms for median time-to-response (TTR), defined as the time from randomization to the observation of an objective (complete or partial) response (22,31). A third retrospective analysis also showed no significant differences between therapy arms with respect to ORR or CB across subpopulations of patients with or without visceral metastases (33).

An unplanned, retrospective non-inferiority analysis was conducted following the failure to show fulvestrant superiority. The non-inferiority analysis was described within original superiority trial reports and was relevant for the outcomes of TTP and ORR. The non-inferiority margin was based on a United States regulatory submissions criterion that the upper CI of the HR for TTP be less than or equal to 1.25 for fulvestrant vs. anastrozole and that the lower confidence limit for the difference of ORR be no worse than -10%. Accordingly, Trials 0020/0021 used a two-sided 95.14% CI that is equivalent to a one-sided 97.57% CI with the addition of 0.07% appropriately adjusting for multiple interim analyses. Evidence from the combined data concluded non-inferiority of fulvestrant according to both the primary endpoint of TTP (5.5 months vs. 4.1 months, HR 0.95, 95.14% CI 0.82-1.10, fulvestrant vs. anastrozole) and the secondary endpoint of ORR (difference in ORR 2.75%, 95.14% CI 2.27-9.05%, fulvestrant vs. anastrozole) (32). To clarify, the upper bound of the 95.14% CI for the HR of TTP (1.10) was less than 1.25 and the lower bound of the 95.14% CI for the difference in ORR (2.27%) was greater than -10%, therefore satisfying the criteria for confirming non-inferiority. There are, however, important methodological issues associated with confirming non-inferiority in trials of superiority design. Please see discussion for full detail.

In actual favour of fulvestrant, the duration of response (DOR), when analyzed for all randomized patients—defined for responders as the time from onset of response to disease progression and for non-responders as zero—was significantly improved at 22.1 months follow-up (ratio of average response durations = 1.30; 95% CI 1.13-1.50, p<0.01) (32). The analysis of DOR among only responders further confirmed this benefit, although significance tests were not reported (16.7 vs. 13.7 months in favour of fulvestrant) (32).

While original publications referring to the combined analysis indicated adjustments of statistical significance levels to account for interim efficacy analysis (32), it is unclear whether subsequent analyses adhered to this standard (see Multiple Reporting in Methods above).

No significant differences in tolerability measures were identified between therapy arms with the lone exception of a higher incidence of joint disorders (including arthralgia, arthrosis, and arthritis) for patients treated with anastrozole (12.8% vs. 8.3%, p=0.0234, anastrozole vs. fulvestrant) (32).

Section 2: EVIDENTIAL BASE
**Fulvestrant versus Exemestane**

There has been one superiority Phase III, multicentre, double-blind, double-dummy, RCT (n=693) by Chia et al. (23) comparing a fulvestrant loading-dose regimen (500 mg IM day 0, 250 mg IM on days 14 and 28, and 250 mg IM injection q [every] monthly thereafter) with exemestane 25 mg orally (po) daily in women with hormone-receptor-positive breast cancer that has recurred on prior adjuvant nonsteroidal aromatase inhibitor (NSAI) therapy (during or within six months of discontinuation) or progressed on prior NSAI therapy for advanced disease (the Evaluation of Faslodex vs. Exemestane Clinical Trial [EFECT]).

Patient and trial characteristics are described in Tables 1 and 2, while efficacy and toxicity measures are described in Tables 3 and 4, respectively. At the time of a final analysis, at a median follow-up of 13 months, there were no significant differences for median TTP (primary endpoint), ORR, CBR, or DOR. Median TTP remained virtually unchanged when adjusted for baseline covariates (see Table 3) (23). Median survival, a planned endpoint, had not been reached at the time of the first planned analysis (23). An abstract presented at the 2007 SABCS (24) provided updated OS data. OS was not significantly different between therapy arms at a median of 20.9 months follow-up (Table 3).

Fulvestrant and exemestane were both well tolerated, with no significant differences noted across any adverse events. Only 2% of fulvestrant-treated and 2.6% of exemestane-treated patients withdrew because of an adverse event. No patient died as a result of a treatment-related adverse event. Quality of Life was measured with the Functional Assessment of Cancer Therapy-Endocrine Symptom (FACT-ES) and Trial Outcome Index (TOI) instruments. The mean difference between therapy arms across both instruments was not significant (23).
Table 3. Efficacy of fulvestrant across included trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment Arms (# Pts)</th>
<th>Outcome</th>
<th>Measure</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median TTP (months)</td>
<td>6.8</td>
<td>HR=1.18 (95% CI 0.98-1.44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8.3</td>
<td>p=0.088&lt;sup&gt;a&lt;/sup&gt; / p=0.137&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Howell et al. (26)</td>
<td>Fulvestrant (n=313) Tamoxifen (n=274)</td>
<td>ORR (%) pts</td>
<td>31.6</td>
<td>OR=0.87 (95% CI 0.61-1.24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>33.9</td>
<td>p=0.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median TTF (months)</td>
<td>5.9</td>
<td>HR=1.24 (95% CI 1.03-1.50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.8</td>
<td>p=0.026&lt;sup&gt;a&lt;/sup&gt; / p=0.039&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median OS (months)</td>
<td>36.9</td>
<td>HR=1.29 (95% CI 1.01-1.64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>38.7</td>
<td>p=0.04&lt;sup&gt;a&lt;/sup&gt; / p=0.12&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median DOR (months)</td>
<td>17.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CBR (%) pts</td>
<td>54.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>62.0</td>
<td>p=0.026</td>
</tr>
<tr>
<td></td>
<td>Fulvestrant (n=428) Anastrozole (n=423)</td>
<td>Median TTP (months)</td>
<td>5.4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>HR=0.94 (95% CI 0.81-1.08)&lt;sup&gt;d,f&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>HR=0.95 (95% CI 0.82-1.10)&lt;sup&gt;c,g&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ORR (%) pts</td>
<td>19.2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Diff. of 2.75% (95% CI 2.27-9.05%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>p=0.31&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>US Phase III Trials 0020 and 0021 combined (22,27,30-32)</td>
<td>Fulvestrant (n=351) Exemestane (n=342)</td>
<td>Median TTF (months)</td>
<td>4.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median TTR (months)</td>
<td>3.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NR&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median OS (months)</td>
<td>27.4&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27.7&lt;sup&gt;e&lt;/sup&gt;</td>
<td>HR=0.98 (95% CI 0.84-1.15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median DOR (months)</td>
<td>16.7&lt;sup&gt;n&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13.7&lt;sup&gt;n&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CBR (%) pts</td>
<td>43.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Diff. of 2.34%, p=0.51&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>EFECT Trial (23,24)</td>
<td>Fulvestrant (n=351) Exemestane (n=342)</td>
<td>Median TTP (months)</td>
<td>3.7</td>
<td>HR 0.93 (95% CI 0.819-1.133)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.7</td>
<td>p=0.65&lt;sup&gt;s&lt;/sup&gt; / HR 0.968 (95% CI 0.822-1.141)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median OS (months)</td>
<td>24.3</td>
<td>HR 1.012 (95% CI 0.833-1.229)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23.1</td>
<td>p=0.9072</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ORR (%) pts</td>
<td>7.4</td>
<td>OR 1.12 (95% CI 0.578-2.18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.7</td>
<td>p=0.736</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CBR (%) pts</td>
<td>32.2</td>
<td>OR 1.03 (95% CI 0.72-1.487)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31.5</td>
<td>p=0.853</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median DOR (months)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>13.5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>9.8</td>
<td>NR</td>
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<td></td>
<td></td>
<td>Median DOR (months)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>7.5</td>
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<td></td>
<td></td>
<td></td>
<td>5.5</td>
<td>NR</td>
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</tbody>
</table>

Statistically significant comparisons are in bold type font.
95% confidence intervals are provided where possible.
<sup>a</sup>Cox proportional hazards model adjusted for baseline covariates.
<sup>b</sup>Cox proportional hazards model unadjusted for baseline covariates.
<sup>c</sup>at median 15.1 months follow-up; original trial report.
at median 22.1 months follow-up.

at median 27.0 months follow-up; original trial report.

95% CI crosses the value of 1.00 and therefore is not significant; therefore, fulvestrant is not superior to anastrozole

95.14% CI in accordance with test for non-inferiority; therefore, fulvestrant is non-inferior to anastrozole

Comparison among responders only.

From the date of random assignment; n=38.

From the date of first response.

Abbreviations: #, number; CB, clinical benefit; CI, confidence interval; Comp, statistical comparison value; Diff., difference; DOR, duration of response; Ful, Fulvestrant; Tam, Tamoxifen; Ana, Anastrozole; Exe, Exemestane; HR, hazard ratio; n, sample size; NR, not recorded; OR, odds ratio; ORR, objective response rate; OS, overall survival; Pts, patients; TTP, time-to-progression; TTF, time-to-treatment-failure; TTR, time-to-treatment-response.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Arm</th>
<th>Hot Flashes (%)</th>
<th>TE Disease (%)</th>
<th>Vaginitis (%)</th>
<th>GI Disturbance (%)</th>
<th>Joint Disorders (%)</th>
<th>Vasodilation (%)</th>
<th>Nausea (%)</th>
<th>Headache (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howell et al. (26)</td>
<td>Ful (310)</td>
<td>17.7</td>
<td>5.8</td>
<td>3.9</td>
<td>37.1&lt;sup&gt;*&lt;/sup&gt;</td>
<td>NR</td>
<td>12.6</td>
<td>4.8</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>Tam (271)</td>
<td>24.7</td>
<td>3.3</td>
<td>6.3</td>
<td>43.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>18.5</td>
<td>8.5</td>
<td>2.2</td>
</tr>
<tr>
<td>US Phase III Trials 0020 and 0021</td>
<td>Ful (423)</td>
<td>21.7</td>
<td>3.5</td>
<td>2.6</td>
<td>48.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NR</td>
<td>NR&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
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<tr>
<td></td>
<td>Ana (423)</td>
<td>22.2</td>
<td>4.5</td>
<td>1.9</td>
<td>45.4&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
<td>combined (32)</td>
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<td>12.8</td>
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<tr>
<td>Gradishar et al. (23)</td>
<td>Ful (351)</td>
<td>8.8</td>
<td>1.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NR</td>
<td>3.4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.7&lt;sup&gt;e&lt;/sup&gt;</td>
<td>NR</td>
<td>6.8</td>
<td>2.0</td>
</tr>
<tr>
<td>EFECT Trial</td>
<td>Exe (340)</td>
<td>11.5</td>
<td>0.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>2.9&lt;sup&gt;d&lt;/sup&gt;</td>
<td>5.6&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>7.9</td>
<td></td>
</tr>
</tbody>
</table>

Statistically significant differences, when reported, are in bold type font with chi-square test p-values indicated.

<sup>a</sup> Includes nausea, vomiting, constipation, and hemorrhage.

<sup>b</sup> Includes anorexia, constipation, diarrhea, nausea, and emesis.

<sup>c</sup> Incidence of venous thromboembolic events

<sup>d</sup> Includes diarrhea only

<sup>e</sup> Includes arthralgia only

Abbreviations: Ana, Anastrozole; Exe, Exemestane; Ful, Fulvestrant; GI, gastro-intestinal; NR, not recorded; Tam, Tamoxifen; TE, thromboembolic.
DISCUSSION

Fulvestrant (Faslodex®), a unique estrogen-receptor antagonist, is gaining recognition as a novel therapy for locally advanced or metastatic breast cancer in postmenopausal women. Despite its therapeutic potential, only a limited body of evidence is available for evaluation, making clinical decisions difficult.

As tamoxifen has historically been the gold standard for first-line therapy for metastatic breast cancer in postmenopausal women, Howell et al. (26) sought to evaluate the use of single-agent fulvestrant as a potential replacement. Results, however, did not argue in favour of fulvestrant as neither fulvestrant superiority nor non-inferiority could be confirmed; the use of fulvestrant saw no significant advantage, and some disadvantage, across all reported efficacy measures reported, including the primary endpoint of TTP (see Table 3). Despite an unplanned, exploratory analysis among patients with tumours both ER+ and PgR+ indicating the potential non-inferiority of fulvestrant, further direct analyses are required to confirm such exploratory evidence. Based on these data, the Breast Cancer DSG cannot support the use of fulvestrant as first-line therapy for metastatic breast cancer—i.e., for patients with no prior cytotoxic or endocrine therapy for advanced disease or no prior adjuvant endocrine therapy—at least when tamoxifen is indicated.

Such evidence is surprising, given that fulvestrant is comparable to third-generation AIs for patients who have progressed on prior tamoxifen therapy (as identified from this review and discussed below) and past studies have found all three third-generation AIs to be at least as good as tamoxifen in first-line metastatic therapy (10-16). Thus, an expected but indirect, associative benefit was not seen. Future studies are needed as the current evidence base is rather limited.

Three Phase III trials compared single-agent fulvestrant to third-generation AIs, namely anastrozole and exemestane, in patients with tumour progression on prior endocrine therapy (23,25,29). Two of these trials—Trial 0020 and Trial 0021, both comparing fulvestrant to anastrozole—were designed to demonstrate the superiority of fulvestrant in terms of efficacy and tolerability. However, the results of a combined analysis did not argue in favour of fulvestrant superiority (32). Such findings should not be taken as evidence of fulvestrant inferiority; indeed, there were no significant differences between therapy arms across numerous efficacy measures including the primary endpoint of TTP (see Table 3), and the subsequent unplanned, retrospective analysis of the combined data yielded a conclusion of fulvestrant non-inferiority (32). Further analyses have also shown a significantly longer DOR among both, therapy responders (30) and non-responders (32), in favour of fulvestrant therapy.

Considering that the majority of patients in Trial 0020 and Trial 0021 had ER+/PgR+ breast cancer (discussed below) with tumour recurrence on prior adjuvant tamoxifen therapy or progression on prior tamoxifen therapy for advanced disease, fulvestrant can therefore be considered a comparable alternative to anastrozole for this patient population. This recommendation remains firm in light of methodological issues identified for Trials 0020/0021 as further discussed below.

Factors that may influence the choice of fulvestrant over anastrozole include a slightly, but significantly, lower incidence of joint disorders and a potential for improved compliance with a monthly injection of fulvestrant over a daily oral pill of anastrozole.

The EFECT trial compared a fulvestrant loading dose regimen to exemestane in women with HR+ breast cancer that had recurred or progressed on prior NSAI therapy. This trial, designed for superiority, found no significant differences across all efficacy, tolerability, and quality of life endpoints, thus indicating that fulvestrant can be considered as an acceptable alternative to exemestane for the trial population.
There are several issues worthy of discussion that may limit the generalizability of EFECT trial findings. First, only 10% of women enrolled received their previous NSAI as adjuvant therapy; thus the results seem more generalizable to women who recurred on previous NSAI therapy for advanced disease (23). In addition, roughly 60% of women received ≥2 endocrine therapies prior to trial therapy (24), and in close to 60% of women, fulvestrant or exemestane was administered as third-line or later therapy (23). Thus, it is unclear as to the optimal sequencing and timing of fulvestrant administration (e.g., second-line, third-line) to derive the utmost efficacy benefit, at least in comparison to exemestane. The EFECT trial authors further indicate that a possible misclassification of patients as AI-sensitive by treating oncologists at the time of prior NSAI therapy could also have contributed to a lowered clinical efficacy and may have undermined the power of the study. To this point, an unplanned retrospective analysis was conducted to compare TTP in patients who both received fulvestrant or exemestane as second-line treatment and who were deemed sensitive to prior nonsteroidal AI. The retrospective analysis showed a non-significant trend in favour of fulvestrant (results were not shown) (23). This suggests that administering fulvestrant in place of exemestane immediately following NSAI failure may provide increased efficacy benefit, although such a hypothesis needs to be confirmed by direct analyses in future trials.

Whether fulvestrant can be considered in place of the other aromatase inhibitors, such as letrozole, currently remains unclear and should be the subject of future trials. Until subsequent trial data are available, no recommendations for fulvestrant in place of letrozole can be made.

There is concern about the methodological rigour of Trial 0020 and Trial 0021 in concluding fulvestrant non-inferiority to anastrozole, as the trials were originally designed for detecting superiority. Trials designed for non-inferiority differ from those designed for superiority, and there are important predefined criteria that need to be considered.

First, fulvestrant is suited for non-inferiority analysis from a clinical policy perspective as the ease of administration versus anastrozole provides a hypothesized secondary benefit if the primary benefits of treatment efficacy are proven comparable.

Second, non-inferiority trials require that evidence from historical reference trials of similar design and setting be reported, or at the very least, direct or indirect evidence that the reference treatment (anastrozole) is showing its usual efficacy should be provided, or else a finding of non-inferiority is suspect (46-50). If the reference treatment, for whatever reason, does not show its usual or historical efficacy, it leaves open the possibility that both treatments, experimental and reference, are equivalent yet ineffective (51). Trials 0020/0021 did not report on any historical data and, further, did not establish that anastrozole showed similar efficacy as previously observed in historical trials. However, the outcomes of TTP and TTF for anastrozole in these trials are comparable to those observed in trials of anastrozole vs. megestrol acetate in second-line therapy for metastatic breast cancer (52-54), when taking into consideration differences in study design and patient population. It is therefore the belief of the Breast Cancer DSG that the efficacy of anastrozole in Trials 0020/0021 was not compromised in any way.

Third, a non-inferiority trial should indicate a prospectively defined margin of difference, that is, the treatment effect beyond which fulvestrant should be no worse than anastrozole (46,48,49,55). Choosing a margin of difference retrospectively may be biased by the observed data. While Trials 0020/0021 failed to prospectively define a margin of difference, they did adopt a criterion used for United States regulatory submissions of hormonal treatments (see Results above). Therefore, the selection of the margin of difference was likely unrelated to the observed data. Furthermore, original reports of Trials 0020/0021 made appropriate statistical adjustments for multiple interim analyses (see Results above). Confirmation of how the United States regulatory submission criterion was derived...
and by whom, however, could not be determined, and thus additional statistical and clinical concerns regarding margin estimation cannot be discussed. Despite this, it is unlikely that the post hoc selection of the non-inferiority margin criterion in these trials invalidates their conclusion of fulvestrant non-inferiority.

Fourth, an analysis should be conducted according to both ITT and per protocol (PP) principles (49,50,56-59). ITT analyses are generally more conservative than PP analyses for investigating superiority. ITT dictates that analyses ignore patients who were not treated according to protocol, in other words, ignore patients who did not comply, crossed-over, or withdrew, for example. Therefore, by analyzing patients according to the original randomization scheme, ITT analyses tend to reduce measured effect sizes. This pragmatic approach is preferable when investigating superiority as this makes a finding of superiority of even greater clinical significance. In the case of non-inferiority, however, this dilution of effect size is anti-conservative, as it will favour a finding of similarity, in other words, non-inferiority. Exceptions to these general behaviours of ITT and PP analyses have been identified (60,61). Therefore, it is important that both ITT and PP analyses be performed. In addition, trials should report rigorously on levels of non-compliance, loss of patients, deviations from intended treatment regimen, and so on, in order to address any differences in the results observed between the ITT and PP analyses and to improve understanding. Trials 0020/0021 were analyzed only according to ITT principles, and measures of patient compliance and follow-up were not reported.

It is the belief of the Breast Cancer DSG that the methodological concerns identified directly above do not invalidate the finding of non-inferiority of fulvestrant in Trials 0020/0021 such that fulvestrant can be considered as a comparable alternative therapy for the target population.

All reviewed trials investigated the use of fulvestrant as a single agent, and no data have been presented on its use in combination with other agents. Therefore, no recommendations can be made at this time regarding the use of fulvestrant in combination with other agents. Currently, there are several trials evaluating the use of concurrent anastrozole plus fulvestrant vs. anastrozole alone in first- or second-line therapy (Southwest Oncology Group [SWOG]-S0226, Fulvestrant and Anastrozole Clinical Trial [FACT], and Study of Faslodex, Exemestane and Arimidex [SOFEA]). As well, a second-line trial (Cancer and Leukemia Group B [CALGB]-40302) is underway comparing fulvestrant alone with the combination of fulvestrant plus lapatinib ditosylate, an epidermal growth factor receptor (EGFR) in human epidermal growth factor receptor inhibitor, in HER2/neu-positive postmenopausal women (see Table 5).

While no studies under review compared the use of first-line fulvestrant to AIs, currently there are two active, ongoing Phase III trials comparing anastrozole alone to anastrozole plus fulvestrant (Table 5) with the hypothesis that total estrogen blockade will be effective in this patient population. No data have yet been released from these trials and thus no conclusions can be drawn.

Across reviewed trials, the standard dose and schedule reported for fulvestrant was a single 250 mg IM injection, delivered monthly into the buttocks (Std). While injections were delivered differently across two trials comparing fulvestrant to anastrozole (two separate 2.5 ml injections in Trial 0020 or a single 5 ml injection in Trial 0021 of 250 mg fulvestrant), a randomized pharmacokinetic study (62) and a pharmacokinetic analysis of Trial 0020 and Trial 0021 (63), comparing between the different modes of injection, found no evidence of pharmacokinetic or tolerability difference suggesting a similar clinical efficacy, although these studies were not likely powered or designed to evaluate efficacy. Contrary to the Std schedule, a loading dose (LD) schedule was employed in the EFECT trial (23) as well as in several ongoing Phase III trials (Table 5). A pharmacokinetic study has shown that dosing with
a single monthly injection of fulvestrant at the standard dosage of 250mg IM can take three to six doses (hence three to six months) to reach steady state levels in the plasma (64). Results from the EFECT trial as reported in original trial reports, and in a more detailed abstract presented at the SABCS 2007 conference, indicate that an LD schedule allowed fulvestrant to reach steady state within only one month of administration (23,24). The only direct comparisons between dosage schedules comes from an MD Anderson retrospective review of 157 consecutive patients receiving fulvestrant that showed no difference in response rate or DOR between patients who had received a single Std injection (n=122) or LD (n=35), thus suggesting similarity (65). However, further prospective, comparative studies are needed to determine what impact, if any, the dosage schedule of fulvestrant has on efficacy. Bearing the evidence in mind, either a standard or loading dose schedule can be used for the delivery of fulvestrant.

As yet, no predictive factors have been reported for the response to fulvestrant therapy. However, Howell et al. (fulvestrant vs. tamoxifen in the first-line metastatic setting) (26) have suggested that patients with hormone-receptor-positive tumours could benefit more so than patients with non-receptor-positive tumours; although primary endpoint analysis indicated that fulvestrant was neither superior nor non-inferior to tamoxifen, an unplanned, subgroup analysis of TTP among patients with tumours both ER+ and PgR+ was consistent with a predefined criterion of fulvestrant non-inferiority. These findings should make intuitive sense as fulvestrant is an ER antagonist and would likely be active only in patients expressing the ER/PgR. Additionally, while two subsequent Phase III trials comparing fulvestrant to anastrozole in patients with tumour progression on prior endocrine therapy failed to stratify efficacy analyses by hormone-receptor status, a greater majority of patients had ER+ and/or PgR+ tumours (81.6% in the combined Trial 0020 and Trial 0021 population (32) and 78.2% in the trial by Howel et al. (26)), perhaps suggesting that a greater majority hormone-receptor-positive breast cancer population influenced these trials' findings of fulvestrant non-inferiority, at least when compared to anastrozole. Similarly, the EFECT trial, in which fulvestrant appears as effective as exemestane, included only patients with hormone-receptor positive breast cancer (23). Further direct comparisons between hormone-receptor-positive and unselected hormone-receptor breast cancer populations are necessary to confirm whether fulvestrant has a place in treating hormone-receptor-negative breast cancer. Therefore, because subgroup analyses based on hormone-receptor status were not consistently evaluated, because the majority of trial participants had hormone-receptor-positive breast cancer, and because fulvestrant is an ER antagonist, it is the view of the authors of this report to maintain the use of fulvestrant in patients with ER- or PgR+ breast cancer, pending any evidence that may suggest otherwise.

ONGOING TRIALS

Ongoing randomized Phase III trials are reported below in Table 5.

CONCLUSIONS

Based on the current evidence base presented in this systematic review, derived entirely from Phase III RCTs, fulvestrant has not been proven to be either superior or non-inferior to tamoxifen as first-line metastatic therapy but may be considered as alternative therapy to anastrozole in the treatment of metastatic breast cancer in hormone-receptor-positive, postmenopausal women who have progressed/recurred on prior tamoxifen therapy. Similarly, fulvestrant may be considered as alternative therapy to exemestane in patients with hormone-receptor-positive and locally advanced or metastatic breast cancer who have progressed on prior third-generation non-steroidal AI therapy. There are, however, important methodological concerns across reviewed trials that clinicians should be aware of, as they may limit the strength of these above conclusions. Whether fulvestrant is comparable to
other AIs, or in other settings, has yet to be determined. Factors that may favour the use of fulvestrant versus anastrozole or exemestane for patients who have progressed on prior endocrine therapy include a decreased risk of joint disturbances (vs. anastrozole only) and improved compliance over an oral therapy.

Table 5. Active Phase III Trials evaluating fulvestrant in at least one arm for the treatment of locally advanced or metastatic breast cancer.

<table>
<thead>
<tr>
<th>Protocol ID and NLM Identifier</th>
<th>First Published</th>
<th>Trial Sponsor</th>
<th>Projected Accrual</th>
<th>Trial Status</th>
<th>Line of Therapy</th>
<th>Arms</th>
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<td>NR</td>
<td>NCI</td>
<td>690</td>
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<td>First</td>
<td>Arm I: Daily Anastrozole. Arm II: Daily Anastrozole + Fulvestrant days 1,14,28 then qmonthly</td>
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<td>D6997L00002, NCT00256698, 9238SW/0001, FACT</td>
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<td>AstraZeneca Pharmaceuticals</td>
<td>558</td>
<td>Active</td>
<td>First</td>
<td>Arm I: Daily Anastrozole. Arm II: Daily Anastrozole + Fulvestrant days 1,14,28 then qmonthly</td>
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<tr>
<td>D6997C00002, NCT00099437, CONFIRM</td>
<td>NR</td>
<td>AstraZeneca Pharmaceuticals</td>
<td>NR</td>
<td>Active</td>
<td>Second</td>
<td>Arm I: Fulvestrant 250 mg qmonthly Arm II: Fulvestrant 500 mg qmonthly</td>
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<tr>
<td>ICR-CTSU-SOFEA EU-20531, EUDRACT-2004-000093-30, ISRCTN44195747, MREC-03677, SSA-04Q200635, NCT00253422</td>
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<td>NSABP</td>
<td>750</td>
<td>Active</td>
<td>Second</td>
<td>Arm I: Fulvestrant days 1, 15, and 29 then qmonthly + Oral Anastrozole once daily. Arm II: Fulvestrant days 1, 15, and 29 then qmonthly + placebo daily Army III: Daily Exemestane</td>
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<td>CALGB-40302, NCT00390455</td>
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<td>324</td>
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<td>Arm I: Lapatinib ditosylate daily on days 1-28 and Fulvestrant days 1 and 15 then qmonthly Arm II: Placebo + Fulvestrant as above</td>
</tr>
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</table>

Abbreviations: SWOG, Southwest Oncology Group; NCI, National Cancer Institute; NCIC, National Cancer Institute of Canada; CALBG, Cancer and Leukemia Group B
CONFLICT OF INTEREST

The authors wish to declare no conflicts of interest as of the date of this report.

JOURNAL REFERENCE

The following systematic review based on this EBS has been published by Breast Cancer Research and Treatment (© Springer Science+Business Media, LLC. 2008; http://www.springerlink.com/content/m4572071p5760767/):


ACKNOWLEDGEMENTS

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For a complete list of the Breast Cancer Disease Site Group members, please visit the CCO Web site at http://www.cancercare.on.ca/

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or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822    Fax: 905-526-6775    E-mail: ccopgi@mcmaster.ca
Appendix A. Combined search strategy applied to Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EBASE

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<tr>
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<td>3 and 4</td>
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Appendix B. Flow diagram of results from literature search strategies.

Figure 1. Flow diagram of literature results from search strategy, up to April, 2008. Cochrane Library of Systematic Reviews, The Canadian Medical Association Infobase, and the National Guidelines Clearing House did not yield any relevant results and thus were not included. 

*Online search strategy available in Appendix B.

Abbreviations: ASCO, American Society of Clinical Oncologists; CENTRAL, Cochrane Central Register of Controlled Trials; EMBASE, Excerpta Medica; MEDLINE, Medical Literature Analysis and Retrieval System Online; SABCS, San Antonio Breast Cancer Symposium
Appendix C: Results of AGREE Tool Quality Rating of Evidence-Based Guidelines

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<th>AGREE Domain Scores</th>
<th>Overall Rating</th>
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<td>Scope and Purpose (%)</td>
<td>Stakeholder Involvement (%)</td>
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<tr>
<td>AGO (21)</td>
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<td>CECOG (19)</td>
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<td>35.4</td>
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<tr>
<td>Puglisi et al. (20)</td>
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<td>6.3</td>
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</tbody>
</table>

Abbreviations: AGO, German Gynecological Oncology Working Group; CECOG, Central European Cooperative Oncology Group.
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28. Jones SE, Pippen J, Webster A. A retrospective analysis of the proportion of patients responding for 1, 1.5 and 2 years in two phase III studies of fulvestrant vs anastrozole [A6047]. Breast Cancer Res Treat. 2004;100 Suppl 1:S236.


34. Jones SE, Pippen J, Webster A. A retrospective analysis of the proportion of patients responding for > 1 year in two phase III studies of fulvestrant vs. anastrozole [A737]. J Clin Oncol. 2004;22 Suppl 14


64. Erikstein B, Robertson JF, Osborne CK, Pippen J, Harrison M. ICI 182,780 (faslodex) 250 mg monthly intramuscular injection shows consistent PK profile when given as either 1 X 5ml or 2 X 2.5 ml injections in postmenopausal women with advanced breast cancer [A2025]. Proc Am Soc Clin Oncol. 2001;20

**Evidence-based Series 1-13: Section 3 (ARCHIVED 2013)**

**Fulvestrant for Systemic Therapy of Advanced or Metastatic Breast Cancer in Postmenopausal Women: EBS Development Methods and External Review Process**

*J. Flemming, Y. Madarnas, J. Franek, and the Breast Cancer Disease Site Group*

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

**Report Date: September 25, 2008**

These guideline recommendations have been ARCHIVED, which means that the document will no longer be tracked or updated but may still be useful for academic or other informational purposes. Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2008 and 2013, and for details on how this Clinical Practice Guideline was ARCHIVED.

**THE PROGRAM IN EVIDENCE-BASED CARE**

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other
stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.
The Evidence-Based Series
Each EBS is comprised of three sections:

- **Section 1: Guideline Recommendations.** Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- **Section 2: Evidentiary Base.** Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- **Section 3: EBS Development Methods and External Review Process.** Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES
Development and Internal Review
This evidence-based series was developed by the Breast Cancer Disease Site Group (DSG) of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on the use of fulvestrant for the treatment of postmenopausal women with locally advanced or metastatic breast cancer developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Report Approval Panel
Prior to the submission of this evidence-based series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel and subsequently addressed included:

<table>
<thead>
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<th>BOX 1: Major issues raised by Report Approval Panel (January 2008)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Issues of multiple reporting:</strong> The authors noted that multiple abstract/article publications exist for Trials 0020/0021. An overarching statement about this issue in the section of Literature Search Results and, if/where appropriate, for given trials would be helpful.</td>
</tr>
<tr>
<td><strong>Methodological concerns of analyzing trial results for non-inferiority when superiority was expected:</strong> In Trials 0020/0021, the Methods sections indicate that the non-inferiority analysis were “not described in the protocol” and were conducted “retrospectively.” The DSG has indicated the retrospective nature of these analyses but could take the opportunity to emphasize the limitations of this approach when trials appear to have been originally designed for superiority.</td>
</tr>
<tr>
<td><strong>The objective of non-inferiority analyses:</strong> From a clinical policy perspective, non-inferiority designs are appropriate when the experimental therapy is hypothesized to have benefits related to secondary outcomes (e.g., quality of life, toxicity, economics, convenience). The experimental therapy may therefore be adopted as a recommended therapy if non-inferiority around major efficacy outcomes is demonstrated (e.g., overall survival, progression-free survival), and a benefit for a secondary outcome is confirmed.</td>
</tr>
</tbody>
</table>
Changes undertaken to address issues raised by Report Approval Panel (January 2008)
- **Issues of multiple reporting**: The authors included a paragraph on concerns regarding multiple reporting in Section 2: Results.
- **Methodological concerns of analyzing trial results for non-inferiority when superiority was expected**: A detailed analysis of methodological concerns and their impact was addressed in Section 2: Discussion. The Breast DSG further provided a consensus statement on how such methodological concerns affect the conclusions and recommendations derived from the evidence in question.
- **The objective of non-inferiority analyses**: Addressed in the point above.

**Practitioner Feedback**
Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

**Methods**
Practitioner feedback was obtained through a mailed survey of 113 practitioners in Ontario (56 medical oncologists, 23 radiation oncologists and 34 surgeons). The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on January 13, 2008. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Breast Cancer DSG reviewed the results of the survey.

**Results**
Thirty-eight responses were received out of the 113 surveys sent (33.6% response rate; 22 medical oncologists, 4 radiation oncologists and 12 surgeons). Responses included returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, twenty-four indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.

**Table 1. Practitioner responses to eight items on the practitioner feedback survey.**

<table>
<thead>
<tr>
<th>Item</th>
<th>Numbera (%)</th>
<th>Neither agree nor disagree</th>
<th>Strongly disagree or disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing a clinical practice guideline, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>22 (95.7)</td>
<td>1 (0.04)</td>
<td>0</td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>19 (79.2)</td>
<td>5 (20.8)</td>
<td>0</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>22 (91.7)</td>
<td>2 (8.3)</td>
<td>0</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>23 (95.8)</td>
<td>1 (4.2)</td>
<td>0</td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>23 (95.8)</td>
<td>1 (4.2)</td>
<td>0</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>23 (95.8)</td>
<td>1 (4.2)</td>
<td>0</td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>20 (83.3)</td>
<td>2 (8.3)</td>
<td>2 (8.3)</td>
</tr>
</tbody>
</table>
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?

<table>
<thead>
<tr>
<th>Very likely or likely</th>
<th>Unsure</th>
<th>Not at all likely or unlikely</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 (79.2)</td>
<td>2 (8.3)</td>
<td>3 (12.5)</td>
</tr>
</tbody>
</table>

For some items, numbers may not total 19 due to missing responses.

For some items, percentages may not total 100 due to rounding error.

Summary of Written Comments
Only five respondents (20.8%) provided written comments. Comments varied. Two comments praised the guideline. One indicated that more study is required. Another pointed that there was no cost-benefit analysis. While a final comment indicated that fulvestrant should also be considered as alternative therapy for letrozole, as letrozole has similar action to anastrozole and exemestane. The respondent further cited that the guideline should address the use of fulvestrant for premenopausal women.

Modifications/Actions and Response to Comments
After reviewing the response rates and comments, the Breast Cancer DSG decided that no further action was required in terms of guideline modification. Without trial data of fulvestrant versus letrozole, no recommendation can be made for such a comparison even in spite of indirect evidence of similar efficacies between letrozole and exemestane or anastrozole. Further, no evidence was available regarding the use of fulvestrant for premenopausal women. The Breast Cancer DSG has decided that the topic will likely be addressed in future updates of this guideline. Lastly, a cost-benefit analysis was outside of the scope of this guideline and was not one of the primary questions that this guideline sought to answer.

Implications for Policy
Based on a draft of this practice guideline, the Breast Cancer DSG submitted funding requests to the Committee to Evaluate Drugs (CED) for fulvestrant as alternative therapy to anastrozole, in postmenopausal women with advanced or metastatic and hormone-receptor-positive (ER+ and/or PgR+) breast cancer that has recurred on prior adjuvant tamoxifen therapy or progressed on prior tamoxifen therapy for advanced disease; and as alternative to exemestane, in postmenopausal women with locally advanced or metastatic and hormone-receptor-positive (ER+ and/or PgR+) breast cancer that has recurred on prior adjuvant nonsteroidal aromatase inhibitor (NSAI) therapy (during or within six months of discontinuation) or progressed on prior NSAI therapy for advanced disease in 2008.

Funding
The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822    Fax: 905-526-6775    E-mail: ccopgi@mcmaster.ca
REFERENCES


Evidence-based Series 1-13: Section 4

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Fulvestrant for Systemic Therapy of Locally Advanced or Metastatic Breast Cancer in Postmenopausal Women: Guideline Recommendations

Guideline Summary Review

Y. Madarnas, S. Craigie, and the Members of the Breast Cancer Disease Site Group

Review Date: September, 2013

The 2008 guideline recommendations are ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario’s Program in Evidence-based Care in 2008.

In December 2012, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (YM) reviewed and interpreted the new. The Breast Cancer Disease Site Group (DSG) ARCHIVED the recommendations found in Section 1 (Clinical Practice Guideline) in October 2013.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1. Compared to tamoxifen and aromatase inhibitors, does fulvestrant improve outcomes for first-line therapy of locally advanced or metastatic breast cancer?
2. Compared to aromatase inhibitors, does fulvestrant improve outcomes for second-line or later therapy of locally advanced or metastatic breast cancer?
3. Compared to therapy alone, does fulvestrant in combination with other therapies improve outcomes?
4. What is an appropriate dose and schedule of fulvestrant?
5. Are there any factors that predict the outcomes of fulvestrant therapy?

**Literature Search and New Evidence**
The new search (June 2008 to January 2013) yielded 40 references, representing 6 guidelines, 3 systematic reviews/meta-analyses, and 12 randomized controlled trials (RCT). 11 RCTs are potentially new studies, of which 8 had full-text publications and 3 were in abstract form. An additional search for ongoing studies on Clinicaltrials.gov yielded 5 potentially relevant ongoing RCTs. Brief results of these searches are shown in the Document Review Tool.

**Impact on Guidelines and Recommendations**
The new data contradicted existing recommendations; there is additional evidence in support of the 500mg dose of fulvestrant. Hence, the Breast Cancer DSG ARCHIVED the 2008 recommendations on fulvestrant in locally advanced or metastatic breast cancer in post-menopausal women.

**Document Summary and Review Tool**

<table>
<thead>
<tr>
<th>Number and title of document under review</th>
<th>1-13 Fulvestrant for systemic therapy of locally advanced or metastatic breast cancer in postmenopausal women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Report Date</td>
<td>February 21, 2013</td>
</tr>
<tr>
<td>Clinical Expert</td>
<td>Dr. Yolanda Madarnas</td>
</tr>
<tr>
<td>Research Coordinator</td>
<td>Samantha Craigie</td>
</tr>
<tr>
<td>Assessment Date</td>
<td>December 11, 2012</td>
</tr>
<tr>
<td>Approval Date and Review Outcome (once completed)</td>
<td>September 17, 2013- ARCHIVED</td>
</tr>
</tbody>
</table>

**Original Question(s):**
- Compared to tamoxifen and aromatase inhibitors, does fulvestrant improve outcomes for first-line therapy of locally advanced or metastatic breast cancer?
- Compared to aromatase inhibitors, does fulvestrant improve outcomes for second-line or later therapy of locally advanced or metastatic breast cancer?
- Compared to therapy alone, does fulvestrant in combination with other therapies improve outcomes?
- What is an appropriate dose and schedule of fulvestrant?
- Are there any factors that predict the outcomes of fulvestrant therapy?

**Target Population:**
Postmenopausal women with locally advanced or metastatic breast cancer.

**Study Section Criteria:**

**Inclusion Criteria**
- Fulvestrant alone or in combination with other systemic agents was evaluated in postmenopausal women with locally advanced or metastatic breast cancer.
- Publication types were randomized Phase II or III trials, clinical practice guidelines, or systematic reviews and/or meta-analyses of randomized trials.
- Locally advanced breast cancers were defined as Stage IIIB or greater.
• Reported outcomes included at least one of the following types of data: time to progression (TTP), time to treatment failure (TTF), objective or complete response rate, progression-free survival, overall survival (OS), compliance/continuation data, and toxicities.

• Clinical trial results were published as peer-reviewed journal articles or publicly available conference abstracts or presentations.

**Exclusion Criteria**

• Trials that were published in a language other than English, as translation capabilities were not available.

• Trials that had not yet reported on evaluable efficacy data and were ongoing at the time of literature searching.

**Search Details:**

• June 2008 to January 2013 (Medline week 3 and Embase week 4)

• June 2008 to February 2013 (ASCO Annual Meeting)

• 2010 to present (SAN annual Meeting)

• June 2008 to February 2012 (Clinicaltrial.gov)

**Brief Summary/Discussion of New Evidence:**

Of 134 total hits from Medline + Embase and 71 total hits from ASCO + SABCS conference abstract searches, 29 references representing 12 RCTs were found evaluating fulvestrant as a first- or second-line treatment for locally advanced or metastatic breast cancer, of which 1 RCT was already included in the existing guideline (rows highlighted in grey in the Table). 11 RCTs are potentially new studies, of which 8 had full text publications and 3 were in abstract form.

**RCTs**

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Name of RCT</th>
<th>Phase of RCT</th>
<th>Population</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulvestrant AD vs LD vs HD</td>
<td>FINDER1</td>
<td>II</td>
<td>Postmenopausal women with LA/ MBC, positive ER status</td>
<td>1: ORR</td>
<td>ORR numerically higher for LD over AD, HD but CI of all 3 overlapped (AD 11.1% (3.7-24.1), LD 17.6% (8.4-30.9), HD 10.6% (3.5-23.1))</td>
<td>Ohno et al 2010</td>
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<tr>
<td>(second line)</td>
<td>(n=143)</td>
<td></td>
<td></td>
<td>2: TTP, CBR, PK profiles, tolerability</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
<td>Median TTP similar 6.0, 7.5, 6.0 for AD, LD, HD, similar number of events</td>
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<td>between groups 30, 31, 31 respectively</td>
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<td>Incidence of AE similar among three treatment arms, no clinically important</td>
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<td>differences in SAE profiles among 3 treatment arms</td>
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<tr>
<td></td>
<td>FINDER2</td>
<td>II</td>
<td>Postmenopausal women with LA/MBC, positive ER status</td>
<td>1: ORR</td>
<td>ORR numerically higher for HD but CI for all 3 overlapped (AD 8.5% (2.4-20.4), LD 5.9% (1.2-16.2), HD 15.2 (6.3-28.9))</td>
<td>Pritchard et</td>
</tr>
<tr>
<td>(n=144)</td>
<td>(34 centres, 8 countries)</td>
<td></td>
<td></td>
<td>2: TTP, CBR, DoR Also PK profiles, tolerability</td>
<td>al 2010</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median TTP lower for AD (3.1) than LD (6.1) and HD (6.0) (months); no. events</td>
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</table>

**Table:**

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<td></td>
<td>Japan</td>
<td></td>
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</tr>
<tr>
<td>FINDER2</td>
<td>(n=144)</td>
<td>II</td>
<td>Postmenopausal women with LA/MBC, positive ER status</td>
<td>1: ORR</td>
<td>ORR numerically higher for HD but CI for all 3 overlapped (AD 8.5% (2.4-20.4), LD 5.9% (1.2-16.2), HD 15.2 (6.3-28.9))</td>
<td>Pritchard et al 2010</td>
</tr>
<tr>
<td>(34 centres, 8 countries)</td>
<td></td>
<td></td>
<td></td>
<td>2: TTP, CBR, DoR Also PK profiles, tolerability</td>
<td>Median TTP lower for AD (3.1) than LD (6.1) and HD (6.0) (months); no. events</td>
<td></td>
</tr>
<tr>
<td>Fulvestrant AD vs anastrozole 1mg (daily), second-line</td>
<td>NCT00327769 (n=234) China</td>
<td>II, double blind, double dummy</td>
<td>Postmenopausal women, ER-positive advanced breast cancer</td>
<td>1: TTP 2: ORR, DoR, CBR, TTF</td>
<td>similar (AD 35, LD 34, HD 31) • Incidence of AE similar across groups (AD 76.6%, LD 72%, HD 69.6%)</td>
<td>Xu et al 2011</td>
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<tr>
<td>Fulvestrant LD vs exemestane (25 mg daily) Second-line</td>
<td>EFECT (n=693) III, randomized, double-blind</td>
<td>Postmenopausal women, hormone-receptor-positive, LA/MBC</td>
<td>1: TTP 2: ORR, CBR, DoR</td>
<td>All analyses done in prospectively defined subgroups: those with and without VM • With VM: TTP similar for F and E (3.1 vs 2.8 months, HR 0.92 CI 0.74-1.13); ORR F vs E 7.1% vs 4.4%, odds ratio 2.69 CI 0.7-4.37 • Without VM: TTP similar for F and E (4.1 vs 5.2 months, HR 1.03 CI 0.8-1.33); ORR F vs E 8.0% vs 11.6%, odds ratio 0.66 CI 0.23-1.80</td>
<td>Mauriac et al 2009</td>
<td></td>
</tr>
<tr>
<td>Fulvestrant LD + anastrozole (1 mg daily) vs Fulvestrant LD vs exemestane (25 mg daily) Second-line</td>
<td>SoPEA (n=723) III, partially blinded randomized</td>
<td>Postmenopausal women, advanced ER+ breast cancer</td>
<td>1: PFS 2: ORR, CBR, OS</td>
<td>No evidence of a difference in PFS; median 4.4 mo (CI 3.4-5.4), 4.8 mo (CI 3.6-5.5), 3.4 mo (CI 3.0-4.6) for F+A, F, and E. • No differences observed for ORR and OS.</td>
<td>Johnston et al 2012 (Abstract)</td>
<td></td>
</tr>
<tr>
<td>Fulvestrant LD + Anastrazole (1 mg daily) vs Anastrazole (1 mg daily) SWOG S0226 (first line) N=707</td>
<td>III, randomized</td>
<td>Postmenopausal women, ER and/or PgR positive, MBC</td>
<td>1: PFS 2: OS, ORR, CBR 3: toxicities</td>
<td>Improved median PFS in combination therapy: 13.5 months A vs 15 months A+F (HR 0.81 CI 0.68-0.94) • Improved OS (median) in combination:</td>
<td>Mehta et al 2012; Mehta et al 2011 (abstract); Mehta et al 2011 (SABCS abstract)</td>
<td></td>
</tr>
</tbody>
</table>
### FACT (second-line) N=514

- **Postmenopausal women, ER/PgR-positive (LA/MBC)**
- **1:** TTP
- **2:** ORR, TTF, DoR, CBR, OS

- **Median TTP:**
  - 10.2 mo A vs 10.8 mo F+A (HR 0.99 CI 0.81-1.20)
- **Median TTF:**
  - 11.4 mo A vs 12.4 mo F+A (HR 1.00 CI 0.83-1.21)
- **ORR:**
  - 33.6% A vs 31.8% F+A (odds ratio 0.92 CI 0.54-1.58)
- **At primary data cutoff, OS:**
  - 37.8 mo F+A vs 38.2 mo A

---

### Fulvestrant HD vs AD Second-line

- **CONFIRM (n=736) (second-line)**
- **Postmenopausal women, LA or MBC**
- **1:** PFS
- **2:** ORR, CBR, DoR, OS, tolerability, QOL
- **3:** Follow-up of OS when 75% patients died (after primary analysis, patients were allowed to switch from AD to HD, all followed to OS)

- **HD significantly prolongs PFS over AD:**
  - HR=0.80 CI 0.68-0.94).
  - Median PFS time 6.5 HD and 5.5 AD. 12 mo 34%HD and 25%AD alive/progression free, at 24 mo 16% and 11%.
- **ORR:**
  - HD 9.1% and AD: 10.2%, odds ratio 0.94 CI 0.57-1.55
- **OS:**
  - median times to death 25.1HD and 22.8AD (months, HR=0.84, CI 0.69-1.03)
- **Follow up:**
  - 8 patients (2.1%) switched from AD to HD. Median OS: HD 26.4 months, AD 22.3 months (HR 0.81, CI 0.69-0.96)

---

### Fulvestrant LD + dasatinib 100

- **SEARCH (n=205) 9 countries**
- **Postmenopausal women, ER+ positive MBC**
- **1:** median PFS
- **2:** ORR, TTP, DoR, DoCB, DoR

- **Median TTP was**
  - 23.4 mo for F vs 13.1 mo for A, 35% reduction in risk of progression (HR 0.66, CI 0.47-0.92)
- **Median TTF was**
  - 17.6 mo vs 12.7 mo for F vs A respectively (HR 0.73 CI 0.54-1.00)
- **ORR:**
  - 36.0% vs 35.5% in F vs A, odds ratio 1.02 CI 0.56-1.87

---

### Fulvestrant LD + dasatinib 100

- **FIRST (n=99) II, randomized, open-label**
- **Postmenopausal women, ER positive MBC**
- **1:** median PFS
- **2:** OS, ORR

- **PFS 6.0 for F+D, 5.3 for F (months)**
- **Median OS 17.0**

---

### Fulvestrant LD + dasatinib 100

- **[unnamed] (n=99) II, randomized**
- **Postmenopausal women, ER+ MBC**
- **1:** CBR
- **2:** Toxicity

- **Doubling AD of fulvestrant does not increase toxicity**
- **Monthly bilateral 5 mL injections well tolerated**

---

### Fulvestrant LD + dasatinib 100

- **[unnamed] (n=99) II, randomized**
- **Postmenopausal women, ER positive MBC**
- **1:** median PFS
- **2:** OS, ORR

- **PFS 6.0 for F+D, 5.3 for F (months)**
- **Median OS 17.0**

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- **Postmenopausal women, ER positive MBC**
- **1:** median PFS
- **2:** OS, ORR

- **PFS 6.0 for F+D, 5.3 for F (months)**
- **Median OS 17.0**

---

### Fulvestrant HD vs ANAstrazole (1mg daily)

- **FIRST (n=205) 9 countries**
- **Postmenopausal women, ER and/or PgR positive, LA/MBC**
- **1:** CBR
- **2:** ORR, TTP, TTF, DoCB, DoR

- **Median TTP was**
  - 23.4 mo for F vs 13.1 mo for A, 35% reduction in risk of progression (HR 0.66, CI 0.47-0.92)
- **Median TTF was**
  - 17.6 mo vs 12.7 mo for F vs A respectively (HR 0.73 CI 0.54-1.00)
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- **Postmenopausal women, LA or MBC**
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- **OS:**
  - median times to death 25.1HD and 22.8AD (months, HR=0.84, CI 0.69-1.03)
- **Follow up:**
  - 8 patients (2.1%) switched from AD to HD. Median OS: HD 26.4 months, AD 22.3 months (HR 0.81, CI 0.69-0.96)

---

### Fulvestrant HD vs AD Second-line

- **CONFIRM (n=736) (second-line)**
- **Postmenopausal women, LA or MBC**
- **1:** PFS
- **2:** ORR, CBR, DoR, CB, OS, tolerability, QOL
- **3:** Follow-up of OS when 75% patients died (after primary analysis, patients were allowed to switch from AD to HD, all followed to OS)

- **HD significantly prolongs PFS over AD:**
  - HR=0.80 CI 0.68-0.94).
  - Median PFS time 6.5 HD and 5.5 AD. 12 mo 34%HD and 25%AD alive/progression free, at 24 mo 16% and 11%.
- **ORR:**
  - HD 9.1% and AD: 10.2%, odds ratio 0.94 CI 0.57-1.55
- **OS:**
  - median times to death 25.1HD and 22.8AD (months, HR=0.84, CI 0.69-1.03)
- **Follow up:**
  - 8 patients (2.1%) switched from AD to HD. Median OS: HD 26.4 months, AD 22.3 months (HR 0.81, CI 0.69-0.96)
mg PO QD  
Vs Fulvestrant  
AD

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Study type</th>
<th>Trialname(s)</th>
<th>Population</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
</table>
| Fulvestrant  (second-line); fulvestrant (third-line) | Meta-analysis (RCT/other experimental studies) | North Central Cancer Treatment Group Trial N0032; EFECT; [FIRST] | Postmenopausal women, HR+ advanced breast cancer | 1: PFS 2: ORR, CBR | • Median PFS 3.9 (80%CI 3.6-5.3) vs 5.7 (80%CI 4.4-7.4) AMG 479 +E/F vs placebo E/F (HR 1.17 80%CI 0.91-1.50) (months)  
• ORR: 8% (80%CI 4-14) treatment arm vs 13% (80%CI 6-23) placebo arm  
• No improvement over placebo for either endocrine therapy | Kaufman et al 2010 (SABCS abstract) |
| Fulvestrant (AD) vs other hormonal agents (anastrozole, exemestane, tamoxifen) | Meta-analysis of RCTs (last update August 2008) | EFECT, [Howell et al], Phase II Trials 0020 and 0021 combined | Patients with advanced breast cancer | 1: OS, TTP, ORR 2: adverse events | • OS: No difference between F and other hormonal agents (HR 1.047 CI 0.688-1.592)  
• TTP: No difference between F and other (HR 0.994 CI 0.691-1.431)  
• ORR: no difference between F and other (odds ratio 1.044 CI 0.828-1.315)  
• No significant difference between F and other for adverse events, deaths due to adverse events  
• F had significantly fewer joint disorders than exemestane or anastrozole (pooled OR 0.621 CI 0.424-0.909) | Valachis et al 2010, Mauri et al 2009 (ASCO abstract) |
| Fulvestrant 250mg (AD) vs Fulvestrant 500mg as first- and second-line therapy | Systematic Review (1980 - last updated Feb 2011) | [Chinese trial]: CONFIRM; EFECT; FACT; FINDER1+2; SOFEA; 0020; 0021; FIRST; | Postmenopausal women with HR positive LA/MBC | 1: ORR, TTP, CBR 2: TTP, ORR, TTF, DoR, CBR, DoCB, OS, QOL 3: Tolerability | Fulvestrant 250mg  
• Second-line: Efficacy as second-line therapy. Compared with anastrozole, no significant difference in TTP or TTF (noninferiority with A reached for TTP and ORR). Median OS not significantly  
• | Croxtall and McKeage 2011 |
different. F 250 of benefit in a compassionate use program: median TTP 3.0-6.4 mo. With loading dose, F250 similar efficacy with exemestane, no difference in TTP, ORR.

- First line: Non-inferiority with tamoxifen not achieved for TTP and survival. ORR not significantly different between F and tamoxifen. TTF significantly greater for T vs F. Median survival significantly longer for T vs F.

Fulvestrant 500mg
- Second line:
  - Clinical efficacy of F 500mg as second-line demonstrated. In FINDER2, ORR doubled for 500 vs 250 mg (stat sig not evaluated). 500mg and 250LD doubled TTP over 250mg. In CONFIRM, TTP significantly longer for 500mg over 250, although ORR and OS not significantly different between 250 and 500g.
  - First-line: 500mg F evaluated vs anastrozole. No significant difference between F500mg and A in terms of ORR. Median TTP significantly favoured F 500 over A.

- Tolerability: both doses generally well tolerated (similar tolerability to anastrazole; no additional issues with 500mg dose vs 250mg)

Clinical Practice Guidelines:

Six clinical practice guidelines that offered a recommendation about fulvestrant use in postmenopausal women were identified.

<table>
<thead>
<tr>
<th>Title</th>
<th>Organization</th>
<th>Year</th>
<th>Summary of recommendations (for fulvestrant)</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Third consensus on medical treatment of metastatic breast cancer | Central European Cooperative Oncology Group | 2009 | For postmenopausal patients with HR+MBC  
- Following tamoxifen failure, 3rd generation AI or fulvestrant recommended for second-line treatment  
- Following failure of 3rd gen NSAI: SAI, tamoxifen, fulvestrant, progestins, estrogen, or androgens may be considered  
- No definitive recommendation for treatment cascade can be given  
- Side-effect and toxicity profiles, and route of admin should be considered in choice of | Beslija et al 2009 |
<table>
<thead>
<tr>
<th>Authors</th>
<th>Title</th>
<th>Year</th>
<th>Summary</th>
</tr>
</thead>
</table>
| Manchon et al | 2010 | Breast Cancer OncoGuia Group (Catalan Cancer Strategy) | 2010 | • In post-menopausal women with MBC, hormone-sensitive, first-line treatment with 3rd generation AIs is recommended  
• In postmenopausal women with disease progression during an antioestrogen treatment, administration of fulvestrant is as effective as anastrozole  
• Fulvestrant is proposed as an alternative second-line treatment |
| Thomssen et al | 2010 | Update 2010 of the German AGO recommendations to the diagnosis and treatment of early and metastatic breast cancer | 2010 | • In postmenopausal women with MBC, fulvestrant in approved dose of 250mg not superior to AIs or tamoxifen as first or second line treatment of MBC  
• Dose of Fulvestrant 500mg superior to 250mg every 4 weeks for PFS  
• First-line fulvestrant HD at least as effective as anastrozole for CBR and ORR, longer TTP  
• Dose of 500mg every 4 weeks (HD) approved  
• No advantage by adding fulvestrant to anastrozole, this combination not recommended |
| Thomssen et al | 2011 | AGO recommendations for diagnosis and treatment of patients with primary and metastatic breast cancer: update 2011 | 2011 | • Hormone therapy remains treatment of first choice for endocrine-responsive MBC  
• 250mg (approved dose) may not be optimal  
• AD, HD, LD have statistically similar efficacy, but AD numerically lower results  
• Fulvestrant is a suitable treatment option for some patients following failure of treatment with prior endocrine therapy  
• Questions remain regarding the optimal dosing regimen between LD and HD  
• HD appears to be as well tolerated as LD |
| Cardoso et al | 2012 | ESMO Guidelines Working Group | 2012 | HR+ LA/MBC  
• Endocrine therapy preferred option except if disease is too aggressive or there are doubts regarding endocrine responsiveness. No rationale for use of combination endocrine therapies  
• Concomitant chemo-endocrine therapy should not be used outside clinical trials  
• In postmenopausal patients, fulvestrant HD has demonstrated superiority compared with anastrozole in first-line setting  
• Second- and further-line endocrine therapy may include (if not already used) tamoxifen, NSAI or SAI, fulvestrant, progestins, and androgens. No definitive recommendation can be given for a specific endocrine treatment cascade  
• Best option after progression on first-line AI therapy is currently unknown |
| Coleman et al | 2012 | NCRI Breast Cancer Study Group | 2012 | The competitive ER antagonist fulvestrant is not recommended in the current NICE guidance  
F is licensed for use in postmenopausal women following treatment failure with AIs  
F should be considered in those with relatively indolent disease with continued endocrine sensitivity, as alternative to chemotherapy  
Hormone therapy is preferred treatment approach for most postmenopausal women with ER-positive advanced breast cancer  
Fulvestrant should be considered after previous responses to both an AI and tamoxifen |

AD=Approved dose (250 mg day 0, 28, every 28 days after)  
LD=Loading dose (500mg day 0, 250mg day 14, 28, every 28 days after)  
HD=high dose (500 mg day 0, 14, 28, every 28 days after)  
LA=locally advanced  
MBC=metastatic breast cancer  
ER=estrogen
receptor; ORR= objective response rate; TTP = time to progression; CBR= clinical benefit rate, PK=pharmacokinetic; CI=95% confidence interval; AE=adverse events; DoR= duration of response; VM= visceral metastases; PFS= progression-free survival; OS= overall survival; PgR= progesterone receptor; QOL=quality of life; DoCB: duration of clinical benefit; HR= hormone receptor

### Active Phase III trials:

Five Phase III trials (4 currently active, 1 completed) registered on or after June 1 2008, evaluating fulvestrant for treatment of locally advanced or metastatic breast cancer in postmenopausal women in at least one arm were identified.

<table>
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<tr>
<th>Protocol ID</th>
<th>Trial Sponsor</th>
<th>Projected Accrual</th>
<th>Trial Status</th>
<th>Line of Therapy</th>
<th>Arms</th>
<th>Outcomes</th>
<th>Results</th>
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<td>NCT01633060</td>
<td>Novartis Pharmaceuticals</td>
<td>615</td>
<td>Active, recruiting as of Oct 2012</td>
<td>Second Arm 1: BKM120 (100 mg once daily)+ Fulvestrant (500 mg (cycle 1 days 1 &amp; 15 and once every cycle thereafter))</td>
<td>Arm 2: Fulvestrant (500 mg (cycle 1 days 1 &amp; 15 and once every cycle thereafter))+ placebo</td>
<td>1: PFS 2: OS, ORR, CBR, AE</td>
<td>Expected Oct 2016</td>
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<tr>
<td>NCT01610284</td>
<td>Novartis Pharmaceuticals</td>
<td>842</td>
<td>Active, recruiting as of Feb 2013</td>
<td>Second Arm 1: BKM120 (100 mg once daily)+ Fulvestrant (500 mg (cycle 1 days 1 &amp; 15 and once every cycle thereafter))</td>
<td>Arm 2: Fulvestrant (500 mg (cycle 1 days 1 &amp; 15 and once every cycle thereafter))+ placebo</td>
<td>1: PFS 2: OS, ORR, CBR, AE</td>
<td>Expected March 2017</td>
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<tr>
<td>NCT01300351</td>
<td>AstraZeneca</td>
<td>220</td>
<td>Active, recruiting as of Feb 2013</td>
<td>Second Arm: Fulvestrant 500 mg i.m. every 28 (+/-3) days plus an additional 500 mg on day 14 (+/-3) of first month only</td>
<td>Arm 2: Fulvestrant 250 mg and matching placebo i.m. every 28 (+/-3) days plus an additional 2 placebo syringes on day 14 (+/-3) of first month only</td>
<td>1: PFS 2: ORR, AE, PK profiles</td>
<td>Estimated March 2014</td>
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<td>NCT00944918</td>
<td>AstraZenica</td>
<td>25</td>
<td>Completed June 2011</td>
<td>Second Arm 1: Fulvestrant (Intramuscular injection on days 1, 15, and 29 and then once monthly) + anastrozole (Tablet, oral, once daily)</td>
<td>Arm 2: fulvestrant (Intramuscular injection on days 1, 15, and 29 and then once monthly)</td>
<td>1: PFS 2: ORR, DoR, CBR</td>
<td>(none posted, no pubs listed)</td>
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### Section 4: Document Review Summary and Review Tool

<table>
<thead>
<tr>
<th>Study ID</th>
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<th>Arm 2</th>
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<td>NCT01602380</td>
<td>AstraZeneca</td>
<td>450</td>
<td>Active, recruiting as of Oct 2012</td>
<td>faslodex 500mg 2 x intramuscular injections at day 1, 14, 28 and every 28 days thereafter, + anastrazole dummy (1 tablet daily)</td>
<td>Anastrazole 1mg daily (oral tablet) + fulvestrant dummy (2 x intramuscular injections at day 1, 14, 28 and every 28 days thereafter)</td>
<td>1: PFS 2: OS, ORR, DoR, DoCB, HRQL, AE</td>
<td>Expected March 2016</td>
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**Notes:**
- ORR = objective response rate; TTP = time to progression; CBR = clinical benefit rate; PK = pharmacokinetic; CI = 95% confidence interval; AE = adverse events; DoR = duration of response; PFS = progression-free survival; OS = overall survival; QOL = quality of life; DoCB = duration of clinical benefit.

### Instructions

For each document, please respond **YES** or **NO** to all the questions below. Provide an explanation of each answer as necessary.

1. **Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?**  
   - **NO**

2. **On initial review,**  
   a. **Does the newly identified evidence support the existing recommendations?**  
   b. **Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?**  
   - **a) YES**  
   - **b) NO.** There is additional evidence in support of the 500mg dose of fulvestrant.

3. **Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations)**  
   - **NO**
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?  

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<td>SEPT 17, 2013</td>
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<td>DSG/GDG Commentary</td>
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New References Identified (alphabetic order):


Literature Search Strategy:
Embase and Ovid Medline (Jan 30):
Ovid Daily/In Process Jan 29

Section 4: Document Review Summary and Review Tool
Ovid: 1996-Jan Week 3, 2013
Embase: 1996-2013 week 4

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ASCO (American Society of Clinical Oncology) (Feb 5 2013):

“fulvestrant” AND “advanced” AND “breast” in title/abstract (manually searched for other inclusion criteria)

SABCS (San Antonio Breast Cancer Symposium) (Feb 6 2013):

“fulvestrant” for 2012, 2011, 2010 (2009 and earlier, abstract view expired) (manually searched for other inclusion criteria)

Clinicaltrial.gov (Feb 20 2013):
Condition: breast cancer AND (locally advanced OR metastatic)
Intervention: fulvestrant OR faslodex
Phase: II or III
Received on or after June 1, 2008
(manually searched for other inclusion criteria)
19 phase II and III studies identified.
OUTCOMES DEFINITION

1. **ARCHIVED** - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the word “ARCHIVED”.

2. **ENDORSED** - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DELAY** - A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. **UPDATE** - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.